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BOARD OF SCIENTIFIC COUNSELORS

HUMAN HEALTH RISK ASSESSMENT (HHRA) SUBCOMMITTEE

Face-to-Face Meeting Summary
Residence Inn Bethesda Downtown
Bethesda, Maryland
November 14–16, 2007

WEDNESDAY, NOVEMBER 14, 2007

Welcoming Remarks and Subcommittee Introduction

Dr. George Daston, Procter & Gamble, HHRA Standing Subcommittee Chair

Dr. George Daston, Chair of the Human Health Risk Assessment (HHRA) Subcommittee, welcomed participants to the Board of Scientific Counselors (BOSC) HHRA face-to-face meeting. He stated that, during this meeting, the BOSC HHRA Subcommittee will conduct a review of the National Center for Environmental Assessment's (NCEA) HHRA Program and will draft a report of the review. He thanked the Subcommittee members for their attendance and the U.S. Environmental Protection Agency (EPA) attendees for preparing the background materials, presentations, and posters for the meeting.

Dr. Daston asked each Subcommittee member to describe his or her affiliation and background. A list of the members and other meeting attendees is attached to this summary.

Dr. Daston said he is a research scientist at Procter & Gamble (P&G) in Cincinnati, Ohio, where he conducts research on mechanisms of toxicity, particularly developmental toxicity, and applied risk assessment. He is responsible for the Human Safety Research Program at P&G. He also is a member of the BOSC Executive Committee.

Mr. Bruce Allen indicated that he is an independent consultant from Chapel Hill, North Carolina. His research experience includes dose response modeling, statistics, and quantitative aspects of risk assessment.

Dr. Richard Corley stated that he is a research scientist at the Pacific Northwest National Laboratory, where he conducts research on toxicology and dosimetry modeling.

Dr. Lauren Zeise said she is Chief of Reproductive and Cancer Hazard Assessment within the California EPA's Office of Environmental Health Hazard Assessment. Her expertise includes dose response modeling and hazard assessment.

Dr. Mark Utell indicated that he is a Professor of Medicine and Environmental Medicine and Director of the Pulmonary/Critical Care and Occupational/Environmental Medicine Divisions at the University of Rochester Medical Center. His focus is on the respiratory health effects associated with the inhalation of materials.

Dr. Daston noted that he asked Dr. Peter Preuss, Director of NCEA, to sit at the Subcommittee table and serve as a spokesperson for any EPA-related questions.

Dr. Daston explained that the Subcommittee had experienced significant attrition. Drs. John Evans and George Lucier are no longer members of the Subcommittee, and Dr. Henry Anderson will not be present for Day 1 of the meeting. Because of the limited number of Subcommittee members, Dr. Daston suggested that the Subcommittee members design a different plan for preparing the report. During the conference call on October 31, 2007, responsibilities had been assigned across each of the HHRA Program's Long-Term Goals (LTGs):

- Drs. Anderson and Lucier were assigned LTG 1.
- Mr. Allen and Drs. Evans and Zeise were assigned LTG 2.
- Drs. Utell and Corley were assigned LTG 3.

Dr. Daston directed the Subcommittee members to the Program Assessment component of the charge question, which consists of several italicized headings: Program Relevance, Program Structure, Program Performance, Program Quality, Scientific Leadership, Coordination and Communication, and Outcomes. He suggested that each Subcommittee member assume responsibility for one or more of the charge components, rather than addressing every charge component for a specific LTG. The Subcommittee members agreed to use the new design plan.

- Dr. Zeise will focus on Program Relevance.
- Dr. Corley will focus on Program Structure.
- Mr. Allen will focus on Program Performance and Program Quality.
- Dr. Utell will focus on Scientific Leadership and Coordination and Communication.
- Dr. Daston will focus on Outcomes.

Dr. Daston explained that a second component of the charge is the Summary Assessment, in which the LTGs are rated and assigned an adjective description. The Summary Assessment is a narrative section, but it is brief and is derived from other sections and the Subcommittee members' deliberations.

During this 2 ½-day meeting, there will be time for the Subcommittee members to draft the report as a group. Dr. Daston stated that Day 1 of the meeting would be comprised mainly of presentations and poster sessions by EPA participants. There will be time on the morning of Day 2 for the Subcommittee members to write individually because the public meeting will not begin until 10:00 a.m. The afternoon of Day 2 and the majority of Day 3 will be set aside for Subcommittee working time.

Dr. Daston remarked that he expects that the Subcommittee members will have developed a relatively complete draft report by the end of the meeting.

Dr. Daston added that the public comment period, originally scheduled for 3:00 p.m. on Day 2, would occur before lunch on Day 2. This is because the Subcommittee received numerous requests for public comment and Dr. Daston wanted to ensure that the meeting agenda did not interfere with the travel arrangements of the participants from the public.

DFO Remarks and Meeting Logistics

Ms. Joanna Foellmer, Designated Federal Officer (DFO), HHRA Subcommittee, Office of Research and Development (ORD), EPA

Ms. Joanna Foellmer, DFO for the BOSC HHRA Subcommittee, welcomed participants to the meeting and thanked the Subcommittee members for their willingness to serve. The BOSC HHRA Subcommittee was created by the BOSC Executive Committee to conduct a review of NCEA's HHRA Program. The Subcommittee members were provided a charge question to which they will respond in their draft report.

The BOSC is a federal advisory committee that provides independent scientific peer review and advice to EPA's Office of Research and Development (ORD). Under the Federal Advisory Committee Act (FACA), all BOSC meetings including more than one-half of the Subcommittee members and involving substantive issues—whether in person, by phone, or by e-mail—are open to the public. Advisory committee documents are accessible to the public, and time is set aside during each meeting for public comment. A *Federal Register* notice must announce all meetings at least 15 calendar days in advance, and an electronic public docket must be established in the Federal Docket Management System. The Subcommittee Chair and DFO must be present at every meeting, and meeting minutes must be certified by the Chair. As DFO, Ms. Foellmer serves as the liaison between the Subcommittee and the Agency and ensures that Subcommittee activities comply with FACA.

The *Federal Register* notice for this meeting was published on October 29, 2007. The electronic public docket can be accessed at http://www.regulations.gov; the docket number is EPA-HQ-ORD-2007-0902.

All Subcommittee members have filed standard government financial disclosure reports and have completed ethics training. Ms. Foellmer has worked with EPA officials to ensure that all appropriate ethics requirements have been satisfied. If conflicts of interest become apparent in any of the topics under discussion, Subcommittee members should inform Ms. Foellmer.

The Subcommittee members have convened for two public conference calls, on October 2, 2007, and on October 31, 2007. This is the first face-to-face meeting. If outstanding issues remain after this meeting, an additional conference call will be scheduled.

When the Subcommittee has completed its draft report, Dr. Daston will submit it to the Executive Committee for review. The Executive Committee will evaluate the draft report, revise it if necessary, and will submit it to the Assistant Administrator (AA) of ORD for consideration.

As Subcommittee Chair, Dr. Daston will conduct the meeting according to the pre-approved agenda, mediate the deliberations of the Subcommittee members, and recognize meeting participants before they speak. EPA staff members are present at the meeting to provide technical information orally to the Subcommittee members as requested under the direction of the Chair. The meeting is not an interactive session between the Subcommittee members and the audience. Because the Subcommittee is providing independent advice and recommendations to ORD, the Agency cannot ask the Subcommittee questions or provide opinions regarding the discussions or conclusions of the Subcommittee members.

A contractor is taking notes and will prepare the meeting minutes. To improve the accuracy of the minutes, speakers should identify themselves and use a microphone when speaking. The minutes will be available on the BOSC Web Site (http://www.epa.gov/osp/bosc) following their certification by the Subcommittee Chair.

The Subcommittee members have received numerous materials for their meeting binders; printed copies of today's presentations also are available to Subcommittee members. Meeting participants can request a CD of the presentations at the registration desk.

This meeting will include three poster sessions. The sessions will be held in a separate room and will allow for one-on-one interactions between Subcommittee members and EPA staff. To comply with FACA, the highlights of each poster session will be summarized and entered into the public record.

Ms. Foellmer received requests from the public to speak during the public comment period. It will be held on Day 2 of the meeting from 12:15 to 12:30 p.m.

If Subcommittee members have completed their travel voucher receipts and homework forms, they should submit them to Ms. Foellmer. If these items are not completed before the meeting adjourns, they can be transmitted to Ms. Foellmer by mail or facsimile after the meeting.

Ms. Foellmer made several remarks concerning logistics for the meeting.

Human Health Risk Assessment: Accomplishing EPA's Mission

Dr. Peter Preuss, NCEA, ORD, EPA

Dr. Preuss thanked the members of the Subcommittee for their contributions to the BOSC review of the HHRA Program. He remarked that the background materials, posters, and presentations had required extensive work and he thanked Ms. Foellmer, Dr. Stan Barone, and Ms. Lynn Papa for their contributions. Dr. Preuss added that Dr. Barone and Ms. Papa are the Assistant Center Directors and they were integral in organizing the materials for the Subcommittee members. He noted that, later in the meeting, HHRA Program clients will provide their perspectives on the program; Dr. Preuss thanked these participants for their attendance.

HHRA Role in Supporting EPA's Mission

Dr. Preuss continued with a discussion of the use of risk assessment in the Agency and HHRA's role in supporting EPA's mission. During the past 30 years, risk assessment has become a central feature of EPA's decision-making process. Currently, most Agency decisions are preceded by an evaluation of risk. Risk assessment has become a useful tool that can be used by risk managers in program offices and regions throughout the Agency to make decisions based on information gathered from published scientific studies.

The use of the risk assessments is worldwide. In 2006, the NCEA Web Site (http://www.epa.gov/ncea) received 8.5 million visits from approximately 120 different countries. Many of these visits resulted in viewers downloading information from the NCEA Web Site.

Risk assessment methodology is becoming increasingly sophisticated and complex. One challenge to NCEA staff is maintaining a working knowledge of the complex field of risk assessment, particularly as new methods are published at a remarkable rate.

The work conducted at NCEA is at the interface between the ORD laboratories and centers and EPA's program offices. NCEA-based products are indispensible for the translation of ORD research for decision-makers. One of the hallmarks of NCEA work products is extensive peer review. This is extremely important to ensure the quality of NCEA's work. In addition, peer review provides NCEA with various perspectives from industrial and environmental organizations and academia during the development process. Often, external scientists will speak to NCEA staff about their risk assessment methodology and results, and this information then is incorporated into the risk assessment documents.

The role of the Office of Management and Budget (OMB) has changed during the past few years. OMB has deemed NCEA products to be of comparable status to regulatory documents. The result is that assessments are reviewed by other federal agencies and OMB, and assessments cannot be published until OMB has provided approval. This differs from prior procedures, and it is one of the significant reasons why the Integrated Risk Information System (IRIS) assessments, one of NCEA's most visible work products, require a long review process.

Dr. Preuss presented a schematic diagram of the current IRIS review process. It depicted the numerous inputs and opportunities for feedback. The process includes document preparation, Agency review, OMB review and clearance, external peer review, a second OMB review, and additional feedback. Dr. Preuss

explained that the process has become elaborate and unwieldy. He noted that IRIS is cited for its low rate of production, but the process precludes speed.

Dr. Preuss noted that NCEA recently had announced completion of 100 percent of its assessments in 2006. On November 13, 2007, however, OMB required NCEA to delete acute risk assessments that NCEA previously agreed to conduct and completed from its completion rate however, did not allow NCEA to lower the total number of completions required. Consequently, the 100 percent completion rate was lowered to 63 percent.

During the Subcommittee conference call on October 31, 2007, a participant asked to what extent NCEA can document its effects on human health and the environment. Dr. Preuss revisited this question, stating that such an assessment is difficult in most circumstances. For instance, the health effect or outcome was documented by the Office of Air and Radiation (OAR). The office found that if the entire country complied with the fine particulate matter ($PM_{2.5}$) standard, for example , between 1,000 and 10,000 fewer people would die from the effects of $PM_{2.5}$. NCEA also can conduct rough estimates of population effect, but these may not be meaningful because they are one step removed from the regulations and OAR. Dr. Preuss emphasized that the assessments that NCEA prepares are used extensively, and the HHRA Program is among those with the most impact at the Agency in terms of public health and the environment.

Discussion

Dr. Utell asked for more information about OMB's ban on acute risk assessments. Dr. Preuss answered that acute assessments are conducted for numerous parts of EPA. For instance, a subset of people may be exposed to a short-term burst of pollutants, and OAR, the Center for Homeland Security, and/or the Department of Homeland Security may need to make informed decisions about health risk and remediation. The HHRA Program has placed high priority on acute assessments and OMB's rationale for prohibiting these assessments was not communicated to HHRA Program staff. Dr. Preuss added that no other programs have taken responsibility for these assessments; instead, they are not being conducted at all.

Overview of LTG 3: Integrated Science Assessments

Dr. Ila Cote, NCEA, ORD, EPA

Dr. Ila Cote, Acting Director at NCEA-Research Triangle Park (RTP) Division, which is responsible for preparing air quality health and environmental assessments known as Integrated Science Assessments (ISAs). Her presentation focused on relevance, quality, leadership, and performance of LTG 3 of the HHRA Program. She also covered basic facts about the air program mandates, LTG 3 achievements to date, and ongoing work.

Program Relevance

The ISAs provide the scientific bases for EPA's air quality regulatory decision-making. NCEA's mission is to integrate and communicate scientific knowledge to support decisions under the Office of Air and Radiation's (OAR) National Ambient Air Quality Standards (NAAQS) program. Six criteria pollutants—ozone, lead, nitrogen oxides (NO_x), sulfur dioxides, PM, and carbon monoxide—were identified in the Clean Air Act (CAA) and serve as the focus of the ISAs.

The CAA mandates the development of air quality health assessments. Dr. Cote set the context of relevance of these assessments by reading an excerpt from the Section 108 of the CAA: "…shall accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable

effects on public health or welfare, which may be expected from the presence of such pollutant in the ambient air, in varying quantities…"
Dr. Cote presented a graphic that showed measures of success in the NAAQS program as a direct measure of the HHRA's success. She stated that the NAAQS program is arguably the most successful environmental program in the world. She cited a 50 percent reduction in pollutants during the past 30 years despite increases in population, energy consumption, travel, and gross domestic product.

Regarding unfinished work for the NAAQS program, Dr. Cote listed the counties for which air quality exceeds the maximum NAAQS pollutant standard (data from 2006). The data indicate that more than 100 million Americans live in counties that are not attaining the standard. Dr. Cote stated that these data can be used for comparisons of epidemiology across each population or benefits analyses of the effects of meeting the PM standard. Ongoing work at NCEA to help populations meet existing standards includes the evaluation of new studies, the application of standards, and the determination of the relevancy of current standards in terms of future projections.

Program Quality and Leadership

Dr. Cote highlighted the rigorous peer review program that NCEA uses for its work products. The Clean Air Scientific Advisory Committee (CASAC), a component of EPA's Science Advisory Board (SAB), is devoted exclusively to the criteria air pollutants, and members of NCEA meet frequently with this committee. In addition, OMB reviews and recommends improvements to NCEA.

Unlike most scientists, NCEA scientists must generate documents that are defensible in court. In 30 years, there has never been an Agency decision overturned because of an error in a scientific assessment, yet each time a standard is re-evaluated, multiple parties sue the Agency. The documents generated by NCEA are a national and an international resource. In 2007, 23,000 copies of LTG3-related documents were downloaded. Moreover, the assessments are highly ranked on computerized search engines.

In addition to generating valuable work products, NCEA scientists must excel in the sciences via the conventional metrics. They hold leadership positions in a number of professional societies, organize workshops, publish and serve on editorial boards of various peer-reviewed journals, and serve as adjunct professors at nearby universities. Last year, NCEA scientists organized a symposium with more than 1,000 registrants.

Dr. Cote detailed the posters that would be presented on LTG 3 activities. She noted that posters 1-6 highlight the New NAAQS process and discuss broad scientific issues that are addressed in the ISAs.

1. "Integrated Science Assessments: The New NAAQS Process." NCEA has both a new process and new products, and this will be presented in the first poster.

2. "Atmospheric Chemistry and Physics Used in Integrated Science Assessments." NCEA acknowledges that the six criteria pollutants are components of a complex mixture of pollutants that impact public health cumulatively. The fate and transport of these mixtures is addressed through the atmospheric chemistry and physics.

3. "Use of Exposure Science in the Integrated Science Assessments." Exposure science further elaborates on the issue of tracing pollutants from emission to exposure and the critical issues that make this process complex.

4. "Dosimetry of Criteria Pollutants in the Integrated Science Assessments." NCEA conducts a dosimetric evaluation for all of its criteria pollutants; this has been critical for species-to-species and route-to-route extrapolations.

5. "Use of Epidemiology and Human Clinical Studies in Integrated Science Assessments." Human data are the most convincing, but epidemiology data also can be useful. These two types of data are very different, but they must be integrated to address the same scientific questions.

Posters 6 through 11 discuss specific criteria pollutants and development of assessments for each.

6. "Particulate Matter Provisional Assessment: Health Effects Literature 2002-2006." In a 6-month period NCEA evaluated several thousand studies to determine how new data in the field of PM related to standard setting. The PM benefits discussed earlier are explained directly in this poster; it details a significant effort to clarify public health effects.

7. "Ozone Air Quality Criteria Document: Mechanisms Underlying Health Effects." Using mechanistic ozone data, one can gain insights into how other pollutants affect health.

8. "Lead Air Quality Criteria Document: Effects below 10 µg/dL." New data on lead may have an impact in standard setting. Past lead standards were set to 10 µg/dL, but new data suggest that this value is too high and a re-assessment may be warranted.

9. "Oxides of Nitrogen Integrated Science Assessment: A Focus on Mixtures." This poster addresses the complex problem of chemical mixtures, specifically NO_x mixtures.

10. "Sulfur Oxides: Evaluating the CxTxR Relationships in a Susceptible Population." Concentration- and time-response relationship information is critical to understanding public health effects in sensitive subpopulations. Yet, concentration is only one factor. This poster highlights the importance of the duration and pattern of chemical exposures. Throughout all of the posters, there is an emphasis on sensitive subpopulations.

11. "Nitrogen and Sulfur Oxides Integrated Science Assessment: Ecological Effects." The broad-range work on environmental effects is showcased in this poster.

12. "Data Resources Supporting Integrated Science Assessments." NCEA is building a database that will explain the process of selecting scientific studies for risk assessments.

Dr. Cote remarked that each poster highlights a particular area within LTG 3 of the HHRA Program, but the posters only represent a sampling of the work conducted under this LTG by HHRA Program staff members.

Program Performance

A top-to-bottom review of the NAAQS process was requested by EPA Deputy Administrator Marcus Peacock in a December 15, 2005 memorandum. An internal working group devised a concept for the new process and meetings were held with the CASAC, stakeholders, and congressional staff. Mr. Peacock issued a final memorandum on December 7, 2006, outlining the revised NAAQS process.

Between 2005 and 2006, the NAAQS process was redesigned, which includes the development of the ISAs. Key to the success of this new process is the close working partnership of NCEA with OAR. The new process can be summarized by four key elements:

1. The integrated plan that guides the effort; NCEA prepares this plan jointly with OAR.
2. The ISAs, which are the most visible of NCEA's products. ISAs also are the focus of the LGT3 APMs.
3. The risk/exposure assessment, led by OAR.

4. The advance notice of proposed rulemaking, which is the first articulation of EPA's plans for standard setting.

Dr. Cote presented a schematic of the new NAAQS review process and pointed out the four major components. She emphasized that only two steps in this complicated process—the first and second drafts of the ISAs—are the only components considered in Annual Performance Measures (APMs). APMs are the public indicators of performance, but they represent just a small portion of the program's efforts, The APMs are a simplistic view of the program's performance. For 2006 and 2007, however, the HHRA Program has met all its APMs under LTG 3.

She also showed the schematic adapted to a single criteria pollutant (ozone). She mentioned that the schematic includes joint efforts with client office, effects assessment, policy standard-setting efforts, and designing of consultation cases. Dr. Cote explained that the technical support NCEA provides to OAR throughout the process is not visible in the schematic, but it is a valuable component that requires much effort.

Dr. Cote illustrated the impacts of the program by presenting an example of recent ozone data. It showed the percentages of children estimated to experience decreased lung function associated with ozone exposure in various cities. At lower proposed levels of the ozone standard, impacts on children were reduced. Dr. Cote noted that the estimate was made based on data in the ISAs.

Dr. Cote summarized that the HHRA Program impacts the entire country, and its success is dependent on the leadership of its staff members and the consistent quality of its outputs.

Discussion

Dr. Daston asked whether CASAC, which works with the HHRA Program on the individual science assessments, has conducted a peer review of the entire program. Dr. Cote responded that CASAC reviews each step in the process and is involved continuously. Dr. Daston remarked that those reviews appeared to be focused on individual ISAs. He wondered if CASAC had reviewed the program on a strategic level analogous to the type of review the Subcommittee was conducting. Dr. Cote responded that the CASAC has not conducted a review such as this one being conducted by the BOSC Subcommittee. Because of CASAC's familiarity with the program, the members might notice issues at a strategic level, but it does not comment on the program's performance.

Dr. Daston remarked that lead is a ubiquitous contaminant; sources include air, water, and land. He asked whether the assessments for different sources are integrated and remarked that standard setting seems to revolve around minimizing blood lead concentration, but reducing the exposure level would be highly dependent on multiple sources. Dr. Cote responded that information about the sources is articulated by NCEA, but it is the role of the program office to determine the extent to which different sources contribute to exposures. She added that Ms. Lydia Wegman, OAR, would talk more about the diverse sources of lead in the United States.

Dr. Utell stated that, in general, a process is changed when the original process is inadequate. Dr. Cote presented a new process, but she used data slides from the previous process of Air Quality Criteria Documents (AQCDs). Dr. Utell commented that he would have appreciated a strategic plan using data from the new process. Moreover, he wondered how the new process compares with the old process, which was incredibly successful. In the AQCDs, each study was peer reviewed; in the ISAs, some studies are weighted more heavily than others. He mentioned that it was not clear how the new process was an improvement, albeit it might allow the program to meet its 5-year goals more easily. Dr. Cote explained that NCEA is required to update its assessment process every 5 years; in the past, the Agency had not been successful with that timeline, and this was the impetus for redesigning the concept. The new process commenced in 2006, and in November 2006, NCEA submitted the first draft ISA to CASAC for review. She explained that data for the new process were not available in time for this meeting, so most of the

slides were derived using data from AQCDs. Dr. Cote was not sure if the new process would make meeting deadlines easier, but she was hopeful that it would. She asked Dr. Utell if he was more interested in comparing the quality of the two processes. Dr. Utell confirmed that quality was his concern; he was unsure if the ISAs were a regression from the AQCDs. Dr. Cote responded that CASAC requested a more concise document. The AQCDs were encyclopedic, and CASAC requested the document be changed so that it focused on the most policy-relevant science. Dr. Utell asked how the two processes will be compared for quality. Dr. Cote responded that the CASAC review will include discussions about how well NCEA captured and weighted the information and how well the Center identified the most policy-relevant studies.

Dr. Corley asked why NCEA appears to be focusing on the exposure to lead in the air. He noted that other sources of lead supersede air exposure. He asked how much duplication of effort exists among the assessments at different sources. Dr. Cote replied that the lead document that NCEA produces is used by EPA for decision-making. The exposure assessments are done by each of the program offices, and program offices use their own documents for assessments. The lead document created by NCEA originally was developed for OAR under the CAA, but it has become more pervasive for all lead exposures since then. Dr. Preuss added that when regulations are promulgated, for instance, for water sources, decision-makers take other sources into account. A participant pointed out that a traditional IRIS assessment was not conducted for lead, instead the IRIS Web Site (http://epa.gov/ncea/iris) points to this document. Ms. Wegman stated that she will address this topic during her presentation. The NCEA document focuses on air-based lead because of the statutory requirement to review and revise standards every 5 years as appropriate. EPA had not reviewed the air lead maximum since 1978, and the Agency considered conducting a review in 1991, but instead prepared an overall lead strategy because lead is ubiquitous. She emphasized that EPA considers the multiple sources of lead in its assessments.

Dr. Zeise asked for the person-years (PYs) involved in the technical aspects of the program. She added that the total PYs were included in the work packets, but she wanted to know the PYs that did not include support staff. Dr. Cote responded that there are only two administrative support staff members in the program. Dr. Mary Ross noted that there are 18 scientists and 2 postdoctoral fellows in the program and they all are full time. She added that the program plans to add five additional technical staff members.

Dr. Zeise asked for more information about the broader process involving stakeholders and the community in terms of evaluating health effects. She asked if the program considered framing questions according to the 1996 National Academies report, *Understanding Risk: Informing Decisions in a Democratic Society*. It might be a useful framework for determining which health effects to study. Dr. Cote replied that the plan is very specific about the policy-relevant questions that researchers are trying to do the science to address. What is not as obvious is their attendance to the NAS recommendations in the report, but they are quite aware of those (e.g., doing more uncertainty analysis) even if that is not reflected clearly in the overall plan.

Poster Session: LTG 3

The Subcommittee reviewed 12 posters in the LTG 3 Poster Session. During the 90-minute poster session, each Subcommittee member had the opportunity to ask questions about the research or clarify specific points with the EPA presenter(s). Poster abstracts and a book of poster reproductions were provided to Subcommittee members before the meeting.

Poster Session Discussion and Questions on LTG 3

HHRA Subcommittee

Dr. Daston explained that the Subcommittee viewed 12 posters detailing various aspects of LTG 3. This included summaries of each of the six criteria air pollutants, various methodologies for assessment of exposure, and the effects of the criteria air pollutants.

Dr. Utell said that the posters were impressive and represented in-depth consideration of the difficult questions surrounding the pollutants. He remarked that carbon monoxide was missing. Dr. Cote responded that the posters focused on a select group of contaminants.

Dr. Utell said that the posters were broad and thoughtful, but he thought they were missing information about the leadership involved in the process, the gaps in information, and the methods for how the scientific studies would be integrated. Specifically, he asked about NCEA's criteria for selecting the most relevant and impactful science. He had noticed that the posters did not showcase work from 5 or more years ago and that certain key studies seemed to be disregarded in the posters. He acknowledged that the program was moving forward but recommended that certain studies continue to be addressed and retained as standards. He compared this session with that of recent nanoparticles meetings he had attended, in which the focus is on the next 5 years. He noted that standards are required before one can gather monitoring data and assess health effects. He summarized his comment by stating that a poster identifying the gaps in the field and suggesting strategies to address the gaps would have been useful and would contribute to forward thinking. Dr. Daston agreed and stated that Dr. Utell could submit that comment as a formal recommendation in the report. He asked Dr. Utell to clarify whether identifying the knowledge gaps and setting strategies was the only recommendation or whether Dr. Utell wanted to mention nanoparticles specifically as a second recommendation. Dr. Utell answered that his recommendation addresses a generic issue, but he noticed a great deal of discussion in the posters about size fractionation of particles, and he brought up that example because he was speculating how nanoparticles work will be conducted given the absence of a long-term strategy.

Mr. Allen stated that, as he viewed each poster, he repeatedly asked the same questions. Specifically, he was interested in the basic science and the approach behind each research project and he wanted information about the expected utility of each project in the context of the ISAs. In addition, he asked EPA staff members about their efforts to integrate the science for the ISAs and, once an approach had been proposed, how the benefit or effect of the approach was measured.

Dr. Corley mentioned that he focused on the overarching process of ISA development as described in each poster. He noted that LTGs are being targeted with these documents and asked how the literature would be evaluated, how studies would be deemed to have an impact, how studies would be categorized, and so on. He explained that the program has six criteria pollutants that it has cycled through during the past few decades. He assumed that NCEA leadership knows the common questions that arise and that it probably structures its ISAs around those questions. He asked how ISAs are composed from studies varying in source, exposure, toxicity, and epidemiology. Dr. Corley summarized that the ISA process needs to be made more transparent. The decisions contributing to the document must be justified and recorded. He also was concerned with the degree to which the ISA can serve two purposes: as a complete analysis of the literature for a scientist in the field and as an executive summary that a manager could read and understand. Dr. Daston responded that the Subcommittee members could recommend more transparency in the process, but he asked Dr. Corley to explain the recommendation in more detail. Dr. Corley answered that ISAs are constructed from a database of perhaps 10,000 entries, and he did not understand the process that NCEA takes to rank or weigh the studies. He clarified that he assumes NCEA documents its thought process, but he did not see any proof of that. He wondered if a mode of action (MOA) framework was available that could be updated as ISAs were prepared. Dr. Preuss responded that there was. Dr. Cote explained that there are criteria involved in the process of preparing ISAs, however, only one ISA exists currently. In the CASAC review, NCEA justified its choices of studies, but CASAC responded that NCEA needed to be clearer about its criteria. Dr. Preuss added that the process is very transparent, but it requires constant communication with experts in the field to identify the key questions and the key studies. The results of these communications are written and translated into a detailed plan of

the focus of the ISA. The document then is peer reviewed. Dr. Preuss added that the plan can be made available to the Subcommittee members. Dr. Daston asked if the plan was available on the Web. Dr. Preuss responded that they have not developed a Web site yet because only one ISA has been completed. Dr. Corley asked about the potential success of the ISA in communicating the science to policymakers and nonscientists. Dr. Cote answered that NCEA has not received feedback yet on the effectiveness of the ISAs for nonscientists.

Ms. Wegman explained that one ISA focusing on NO_x has been reviewed by CASAC. The CASAC recommended increased transparency in the study selection process.

Dr. Zeise cited the 1996 NAS *Understanding Risk: Informing Decisions in a Democratic Society* document. It addresses the engagement of the nonexpert community prior to consulting experts. She asked if such a process has been tested in the program, and if not, whether it seems useful given the program's limited resources. Dr. Cote answered that public notice of the process is published in the *Federal Register*, but there is little public participation. Town meetings are organized to discuss specific problems, but the program is not proactive in engaging the public to contribute to the ISA process. Ms. Wegman clarified that, during a proposed ruling, members of the public submit comments about the risks that are of concern to them. Under the new process, advance notice of a proposal is published so that members of the public will have an opportunity earlier in the process to offer their opinions through public hearings or written comments. Dr. Zeise asked if public comments affect the direction of the research during the 5-year cyclical process. Ms. Wegman agreed that they should. Dr. Cote added that NCEA used to create a research document that provided full disclosure, but because of budgetary concerns, that valuable document has been discontinued.

Dr. Zeise asked if the program documents its experiences from one review session in preparation for the next. Dr. Cote responded that there currently is no formal process in place to do so. A participant from EPA explained that the program works closely with Dr. Daniel Costa, the National Program Director (NPD) for air research. The NPD is familiar with the questions that arise during the ISA process, which allows for a feedback loop to the research planning process. It does not influence NCEA or HHRA resources, but it does influence the resources for ORD bench scientists. Thus, feedback does exist, but it is based on interactions and experiences with other EPA and external scientists rather than on a document. Dr. Cote added that there is a Multi-Year Plan (MYP) that the NPD prepares for OAR, and it is publicly available.

Dr. Zeise noted that she was interested in how the process is translated to benefits assessment. She recalled a poster that showed a variety of outcomes, but it lacked confidence intervals and narrative descriptions about uncertainty. She noted that this information probably exists but was not captured in the posters. Dr. Cote replied that OAR conducts benefits analyses, but ORD does not. Ms. Wegman added that she would address Dr. Zeise's question during her presentation.

Dr. Daston asked how much interaction occurs between the staff members who write the ISA and the rest of the Agency. He noted that there clearly is interaction with the client for each product, but it also would seem that input from researchers throughout the Agency could be valuable to the staff members preparing the ISAs if questions arise. He asked if these staff members are in close contact with the National Exposure Research Laboratory or the National Health and Environmental Effects Research Laboratory, and if so, how much time is spent gathering information from researchers who work more closely with the public and on implementation. Dr. Utell stated that his experience with criteria reviews indicates that the staff members who write the ISAs are highly integrated with other EPA researchers. He pointed out that the staff are co-located in one building and interact frequently. The posters indicated this integration. In one poster, ozone exposure was depicted as a process, with steps described from early changes in lung function to death. He noted, however, that health effects seem to be isolated from exposure. For instance, a person may be at risk of mortality, but if they remain indoors, there is virtually no exposure. He summarized that there seems to be extensive collaboration throughout the Agency, but in the cases of

high uncertainty, he wondered if that collaboration was maintained. Dr. Cote explained that staff members attend regular research coordination meetings, led by Dr. Dan Costa, the National Program Director for ORD's Air Quality Program and MYP. She added that, in addition to the NCEA staff, the posters presented were co-authored with staff from the program office and researchers from ORD labs. This is emblematic of the collaboration. Dr. Preuss stated that another example of how assessments and research are integrated under ORD's Air Quality Program is the five PM research centers at universities, which have received long-term grant funding. The work among these centers is integrated, and all of the staff members who work on the assessments and at research centers discuss their work frequently. He stated that this program is perhaps the one area of ORD where integration is most successful. Dr. Cote added that the integration is evident in terms of the success of the program and the fact that funding has remained sufficient for the program's success.

Dr. Zeise asked about the program's assignment of indicator chemicals or indicator substances. She recalled a poster discussing NO_x and NO_2 in which NO_2 was an indicator chemical. She stated that PM may be used as an indicator of numerous other chemicals, and control of PM could be extrapolated to control of many other contaminants. She remarked that there is constant criticism regarding the inappropriate use of indicator chemicals, and she was interested in which other pollutants were assigned as indicators. Dr. Cote answered that all of the criteria pollutants, with the exception of carbon monoxide, could be deemed indicators, but this is an overly simplistic view from a scientific standpoint.

Overview of LTG 1: IRIS and Other Priority Health Assessments

Dr. Abdel Kadry, NCEA, ORD, EPA

Dr. Abdel Kadry is the Director of the IRIS Program. He stated that the mission of EPA is to protect public health and the environment. To accomplish this, EPA programs and offices set standards and regulations to reduce the contaminants in the environment. HHRA is a unique program that offers scientific information and support to inform decision-making in EPA program offices and regions.

Program Context

Dr. Kadry presented a diagram that depicted the three components of LTG 1: IRIS, provisional peer-reviewed toxicity values (PPRTVs), and incidence response.

Program Relevance

IRIS and PPRTVs provide EPA with the scientific positions on potential adverse health effects that may result from exposure to chemical substances found in the environment. The IRIS database contains data on more than 540 chemicals. IRIS is used by EPA program and regional offices; federal, state, and local agencies; international agencies; and the public, which includes academia, regulated industries, environmental organizations, and individuals. In many cases, these audiences rely primarily on IRIS to inform their responses. There were between 7.4 and 8.7 million visits per year to the IRIS Web Site from 2004 to 2006.

The toxicity values from IRIS and PPRTVs are combined with problem-specific exposure information to develop risk estimates. These risk estimates are the scientific input EPA decision-makers use in setting standards for the release of chemicals to air, water, and land; determining safe clean-up levels at contaminated sites, and setting allowable levels of chemical residues in food and drinking water, consumer products, and indoor and outdoor environments. The four steps involved in risk assessment include: (1) dose-response assessment; (2) hazard identification; (3) exposure assessment; and (4) risk characterization. The development of IRIS and PPRTV toxicity values constitute the first two steps, while the application of these values to specific exposure scenarios and the identification of the assumptions and uncertainties constitute the remaining two steps.

Program Quality and Leadership

Dr. Kadry identified a number of HHRA Program quality and leadership indicators. IRIS assessment milestones achieved from 2005 through 2007 include: the submission of 36 draft assessments for Agency review, submission of 36 draft assessments for interagency review, 12 draft assessments posted for public comment and external peer review, eight assessments posted on the database, and a National Academies review of key issues in the trichloroethylene (TCE) assessment. PPRTVs for more than 100 chemicals were provided to the Office of Solid Waste and Emergency Response (OSWER) from 2005 to 2007. In addition, the program has incorporated application of 2005 cancer guidelines, age-dependent adjustment factors, and new methods developed under LTG 2 into several recently completed and ongoing IRIS assessments to ensure that the assessments reflect the most current state of science.

Dr. Kadry presented a diagram indicating that HHRA toxicity values (IRIS and PPRTV) are used in 84 percent of Superfund baselines assessments. In addition, HHRA toxicity values were used for EPA's 1999 National Air Toxics Assessment (NATA) of the nationwide health risk estimates for air toxics. Dr. Kadry indicated that 69 percent of the toxicity data for the 1999 NATA came from IRIS and 27 percent from PPRTVs. He directed the Subcommittee to Poster 12, "Human Health Risk Assessment Products: Outreach, Use, and Impact," for more discussion about these issues.

Hierarchy for Supporting Superfund

Office of Superfund Remediation and Technology Innovation (OSRTI) Directive 9285.7-53 identifies a hierarchy of sources for toxicity information used in Superfund site assessments. Tier 1 of the hierarchy is IRIS values. If IRIS values are not available, PPRTVs are used (Tier 2). Other toxicity values that are peer-reviewed, transparent, and publicly available, such as California EPA's toxicity values or the Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Levels (MRLs) will be used when both IRIS values and PPRTVs are unavailable (Tier 3).

Process for Developing an IRIS Assessment

The development of an IRIS assessment is a multi-stage process that includes three key stages: (1) development of the IRIS agenda and draft toxicological review/IRIS summary and internal peer review by NCEA; (2) external peer review and public comment, which includes peer review by EPA, other federal agencies, OMB, public comment, and other external sources; and (3) clearance from the Agency and OMB and posting of the final assessment on IRIS. Dr. Kadry noted that Poster 1, "Integrated Risk Information System (IRIS)," describes the IRIS assessment development process in detail.

Process for Developing a PPRTV Assessment

The PPRTVs that are provided for specific use of the Superfund program follow a less complex process than that for IRIS. OSRTI prioritizes the new chemicals and updates in the queue. The PPRTV process consists of: (1) development of a draft internal review document prepared by a Chemical Manager; (2) internal and external peer review, which includes reviewers from all NCEA Divisions and an independent external review (three reviewers); (3)) preparation of a final draft document that includes the resolution of comments; and (4) submission of the draft for clearance through the Superfund Health Risk Technical Support Center (STSC) Director, NCEA Division management, and the NCEA Director. The PPRTV assessment then is submitted to Superfund. Dr. Kadry noted that Poster 2, "Provisional Peer-Reviewed Toxicity Value Documents (PPRTVs)," describes the process for developing PPRTV assessments.

Incidence Response Assessment Activities

Poster 3, "Incidence Response Assessment Activities," explains the program's efforts during national emergencies involving potential risks to human health from exposures to environmental contaminants. EPA scientists in ORD's HHRA Program have played a significant role in responding to these unfolding situations. Often, the combination of contaminants, the routes and patterns of exposure and other aspects of the emergency are unique and require creative solutions. Human health risk and exposure assessments, both quantitative and qualitative, often are needed to scientifically address questions of risks to human health. Dr. Kadry mentioned one of the recent assessment challenges faced by HHRA Program staff was the potential human health impacts from the incineration of debris, including asbestos, from the aftermath of Hurricane Katrina, 2005. The EPA clients for this assessment were Region 6, Office of Water, Superfund, Office of Emergency Response, and Office of Air.

LTG 1 Posters

Dr. Kadry identified the posters and presenters for LTG 1:

#1: Integrated Risk Information System—Samantha Jones, Presenter
#2: Provisional Peer-Reviewed Toxicity Value Documents (PPRTVs)—Jon Reid, Presenter
#3: Incidence Response Assessment Activities—Danielle Devoney, Presenter
#4: IRIS Acrylonitrile Assessment—State of the Art Assessment, Diana Wong, Presenter
#5: Use of Epidemiologic Data in IRIS Assessments—Glinda Cooper, Presenter
#6: Linear and Nonlinear Approaches for Human Health Risk Assessment—Reeder Sams, Presenter
#7: Assessment of Early-Life Exposures and Application of Age-Dependent Adjustment Factors (ADAFs) to Chemical Carcinogens with a Mutagenic Mode of Action—Channa Keshava, Presenter
#8: Physiologically-based Pharmacokinetic (PBPK) Model Applications in IRIS—Rob Dewoskin, Presenter
#9: Benchmark Dose Modeling and its Applications in EPA Chemical Assessments—Jeff Gift, Presenter
#10: Characterizing Uncertainty in IRIS Assessments—Karen Hogan, Presenter
#11: Concentration x Time Response Relationships—George Woodall, Presenter
#12: Human Health Risk Assessment Products: Outreach, Use, and Impact—Gary Foureman and Mike Troyer, Presenters

In addition to the three posters highlighted previously, Dr. Kadry described key points discussed in the remaining posters. Poster 12 addresses the outreach, use, and impact of human health assessment products. Posters 4-10, represent the new methodologies used in the IRIS assessments.

Poster 4, "IRIS Acrylonitrile Assessment: State of the Art Assessment," provides an example of the application of state-of-the-art methodologies and newer scientific information in an assessment. Methods and information evaluated include: cancer and noncancer epidemiological studies; evaluation and modification of available physiologically based pharmacokinetic (PBPK) models for AN and its reactive metabolite in rats and humans; use of benchmark dose modeling; derivation of the inhalation unit risk taking into account temporal changes in the exposure in extensive epidemiological data; evaluation of MOA for the carcinogenicity; and quantitative adjustment for carcinogenic response to early-life exposure.

Use of MOA Data to Inform the Quantitative Approach for Low Dose Extrapolation of Risk

Poster 6, "Linear and Nonlinear Approaches for Human Health Risk Assessment," describes the MOA framework for published information. MOA considerations are critical in developing low dose extrapolations in human health risk assessments. Implementation of EPA's 2005 *Guidelines for Carcinogen Risk Assessment*, commonly known as the 2005 Cancer Guidelines, has highly influenced human health risk assessments that are in progress or that have been recently completed. Currently,

NCEA scientists are addressing concerns with common MOAs, low dose additivity to background, and inter-individual human variation in order to improve these considerations in risk estimates.

Use of Epidemiologic Data in IRIS Assessments

Epidemiological data can provide important information for risk assessments; however, maximizing the utility of epidemiological data can be a challenge. Poster 5, "Use of Epidemiologic Data in IRIS Assessments," addresses the question: Can epidemiologic data be used to ensure that the most susceptible populations among our population are protected from harm? The poster also describes the methodology of incorporating epidemiologic data into IRIS assessments. Also discussed is how human and animal studies can provide complementary information and the challenge to maximize the usefulness of each discipline. The use of epidemiologic data by NCEA scientists for insight into potential MOAs and other biological issues with respect to exposure and disease is discussed. Epidemiologic data also may be used to contribute to identification of hazards and derivation of accurate toxicity values.

Benchmark Dose Modeling and Its Application

During late 1980s and early 1990s, NCEA scientists employed No Observed Adverse Effect Levels (NOAEL) and Lowest Observed Adverse Effect Levels (LOAEL) approach for dose-response assessment. EPA now routinely uses benchmark dose (BMD) methodology for both cancer and noncancer assessments. This approach helps quantify uncertainty in the database and generates points of departure from which toxicity values are derived. The BMD approach provides several advantages over the NOAEL (and LOAEL) approach including being less dependent on the doses used within a study and penalizing studies of poor quality (e.g., small sample size) by generating lower PODs. Poster 9, "Benchmark Dose Modeling and Its Application in EPA Chemical Assessments," discusses these issues.

Key Questions in Application of Age-Dependent Adjustment Factors to Chemical Carcinogens

Poster 7, "Assessment of Early-Life Exposures and Application of Age-Dependent Adjustment Factors (ADAFs) to Chemical Carcinogens with a Mutagenic Mode of Action," describes supplemental guidelines for assessing susceptibility of infants and children, in which early lifetime exposure adjustments may be applied to the cancer potency value of chemical carcinogens. The key questions are: Is the hypothesized MOA sufficiently supported in the test animals? Is the hypothesized MOA relevant to humans? Which populations or life stages can be particularly susceptible to the hypothesized MOA?

Concentration x Time Response Relationships

What is the best method for duration extrapolations? Poster 11, "Concentration x Time Response Relationships," describes the methodology for these types of assessments. Reference values for less-than-lifetime durations are key in determining allowable short-term exposures during emergency response and clean-up situations. Extrapolation from experimental observations to health effect reference values at another duration often is necessary. For example, in an acute timeframe, a 4-hour exposure may need to be converted to durations as short as 30 minutes or as long as 24 hours. Also, in a typical chronic reference concentration (RfC) derivation, experimental exposures of 6 hours/day, 5 days/week for 90 days will be converted to a continuous exposure of 24 hours/day for a lifetime. NCEA has developed methods for assessing health risks from acute and short-term inhalation exposures and applied them in assessments for hexachlorocyclopentadiene (HCCPD), acrolein, ethylene oxide (EtO), hydrogen sulfide (H_2S), and phosgene. These assessments explore several issues including the relevance of lethality to less severe endpoints (e.g., irritation, neurotoxicity), duration extrapolation for data-limited chemicals, and application of CatReg analysis. General issues discussed include dosimetry, estimating a time to recovery following an acute exposure, and toxicokinetic/toxicodynamic considerations when validating extrapolations from observed data.

Physiologically-based Pharmacokinetic (PBPK) Model Applications in IRIS

Poster 8, "Physiologically-Based Pharmacokinetic (PBPK) Model Applications in IRIS," describes how PBPK models are used in lieu of default adjustment factors or to bridge data gaps in the derivation of IRIS reference values. Adequately developed, tested, and evaluated PBPK models are being used to improve the scientific support and availability of IRIS reference values by replacing default adjustment factors for interspecies or intraspecies toxicokinetic differences that would impact the response to a given dose. PBPK models also provide a means to extrapolate an observed dose-response relationship from one route or duration of exposure to another when data are limited.

Characterizing Uncertainty in IRIS Assessments

Risk managers at the federal, state, and local levels as well as the public can benefit from an improved understanding of uncertainty in the scientific data and methods used to assess hazard and dose-response. By understanding uncertainty in risk assessment, risk assessors and managers are better able to make decisions, set priorities, and allocate resources most effectively. A significant issue in IRIS assessments is characterization of this uncertainty, particularly when some of the uncertainty is known and some is unknown. This challenge is discussed in Poster 10, "Characterizing Uncertainty in IRIS Assessments."

Conclusions

Dr. Kadry concluded that ORD will continue to work to improve the performance, coverage, and quality of the research to support LTG 1. The HHRA Program under LTG 1 plans to: (1) increase the rate of posting of assessments on the IRIS database to 16 per year by 2010; (2) update all IRIS assessments more than 10 years old for which new studies might support a revised toxicity value; and (3) complete 50 new or updated PPRTVs for the Superfund Program per year. To achieve these goals, the program will: (1) increase production of IRIS assessments and PPRTVs; (2) accelerate the updating of IRIS assessments that are more than 10 years old and have been identified as having new data that could change a toxicity value or cancer descriptor, and (3) incorporate new state-of-the-science methods as they become available and maintain high quality through rigorous peer review.

Discussion

Dr. Zeise asked about a poster that discussed hierarchy in IRIS values, PPRTVs, and values from other sources. It also included a discussion of screening values that were not used for regulation but were used for priority setting. She asked for more information about the screening values and how they fit into the hierarchy. A participant from EPA responded that the screening values are produced in cases in which there are insufficient data to derive a dose response equation, but there is some information that is potentially useful for the Superfund staff. Rather than withholding the information until more becomes available, screening values are published in an appendix of the document. These values are not part of the standard dose response equations. The hierarchy was defined by the Superfund Program to attain consistency across the United States. Dr. Zeise suggested that the screening values address information gaps. When Dr. Kadry had mentioned the percentages of chemicals covered by IRIS or PPRTVs, she would have appreciated data regarding the chemicals for which values are not available but needed. An EPA participant responded that the data Dr. Kadry presented were derived from requests that the program received from the Superfund staff. When regional managers identify chemicals at waste sites, they request values, but if no values are available, the chemicals are disregarded from the Superfund process. The value (i.e., 84 percent) indicated that, of the chemicals for which values exist, 84 percent of those values were derived from IRIS values or PPRTVs. Dr. Kadry did not indicate that, of all the chemicals detected at the Superfund sites, 84 percent of them had pre-existing values. Dr. Zeise commented that NCEA could examine programs to determine what fraction of pollutants is being addressed with the IRIS values and PPRTVs.

Dr. Preuss remarked that the arithmetic presented on the slides is incorrect. Assuming that there are 540 chemicals in the IRIS database, 70 assessments would need to be completed each year to maintain the proposed rate of renewals, but NCEA instead is generating 16 assessments per year. This is a major issue. For PPRTVs, the process is less complex and values are published at a higher rate.

Dr. Zeise asked for a description of the program resources, including full-time scientific and technical staff and contractors. Dr. Preuss explained that there are 65 staff members across NCEA who contribute to IRIS assessments. He was not sure of the exact value of the contract funding but estimated it to be approximately $7 million. He added that the funding fluctuates and largely is devoted to document preparation and peer reviews. Dr. Corley asked whether the scientific staff contribute to IRIS exclusively. Dr. Preuss answered that approximately 30 staff members work exclusively on IRIS assessments. The others work part-time on IRIS. This translates to 65 full-time equivalents (FTEs).

Dr. Daston asked how IRIS assessments are prioritized. He recalled a slide showing the queue for chemical priority, but he wondered which factors contribute to prioritization. Dr. Kadry responded that chemicals are nominated by the Agency and by the public. Depending on the number of nominations and the availability of information for the assessment, a chemical will receive a priority ranking. Dr. Daston asked if the rankings are published. Dr. Preuss replied that there was a public meeting that focused on prioritization. The process is straightforward, and he will make it available to the Subcommittee members. Dr. Utell asked how much the priorities fluctuate each year. Dr. Kadry explained that the PPRTV lifespan is 5 years. After that time, the values expire. For IRIS, originally there was no expiration date, but now IRIS assessments will expire after 10 years. Dr. Utell clarified that the question pertained to how chemicals to be assessed are chosen. He wondered if there was a plan for the years ahead or if the prioritization was updated every year. Dr. Kadry responded that the plan is updated each year; the program receives nominations each year and updates its assessment plan accordingly.

Poster Session: LTG 1

The Subcommittee reviewed 12 posters in the LTG 1 Poster Session. During the 75-minute poster session, each Subcommittee member had the opportunity to ask questions about the research or clarify specific points with the EPA presenter(s). Poster abstracts and a book of poster reproductions were provided to Subcommittee members before the meeting.

Poster Session Discussion and Questions on LTG 1

HHRA Subcommittee

Dr. Utell stated that the posters were well done. He commented on the sense of continuity and process regarding how EPA views the IRIS process. He noted that the one poster, describing outreach, intrigued him because he had believed that IRIS did not need outreach. Based on the number of visits to the IRIS Web Site, it appears that many and diverse audiences are using the database. He asked about the 5-year planning process for the IRIS assessments. He was surprised to find that the prioritization was not a random event but was based on information from parties that respond to the request for nominations. He commented that it did not seem like an Agency-oriented process, in which chemicals were chosen based on their importance to EPA. He asked Dr. Kadry to address why there are no priority chemicals over a multi-year process and commented that the nomination-based procedure contrasts with the ISAs, whereby statutes require the same materials to be reassessed every 5 years. It seems as though there should be a plan for future IRIS assessments, but he did not see one. Dr. Kadry answered that IRIS is a service program. It services the needs of EPA programs and offices first and the public second. When NCEA requests nominations and perspectives, it compares the nominated chemicals to the criteria that are important to the EPA programs and offices to fulfill the needs of both parties.

Mr. Allen asked about the consistency of the nomination process. He wondered if there was continuity in the assessments such that EPA had a sufficient estimate of the multi-year outlook. Dr. Kadry responded that there are 540 chemicals already in the database, and these are re-assessed periodically. Unless the nominating parties know of additional chemicals that are new or were not chosen for assessments the previous year, they do not have to submit nominations. Mr. Allen remarked that it may not be necessary to renew the nominations each year. Dr. Preuss explained that the complex set of interactions contributing to the nominations was being oversimplified. Program offices identify chemicals for which they know there is extensive exposure and the potential for toxic effects. The offices nominate these chemicals if they think a decision should be made about whether to regulate the chemicals. There are pre-existing criteria related to public health, risk exposure, and so on, and the nominated chemicals generally are included in these criteria. Secondly, there are some chemicals that seem to be of overarching importance. There are plenty of exposure and toxicological data for these chemicals, and multiple parties are concerned about the health effects. There are about 12 chemicals in this category, and they tend to be reassessed periodically in light of new data. One example is perchloroethylene, which has been assessed three times in 20 years. Lastly, NCEA determines if the nominated chemicals are members of a larger family of chemicals. For instance, NCEA conducted an assessment on the phthalate compounds as a family because many of these compounds exhibit the same MOA and/or result in the same endpoint effects on male reproduction. NCEA works with the National Academies for guidance on identifying chemical families.

Dr. Utell pointed out that if a chemical is nominated but not chosen for an assessment, it might be overlooked. Dr. Preuss agreed and added that ideally, the program would increase the number of chemical assessments. In addition, the HHRA Program needs to prioritize how readily it re-assesses the existing chemicals in the IRIS database.

Dr. Zeise commended the program's impressive poster session. She noticed the sensitivity and understanding that surrounds the major risk assessment issues. She asked how the program addresses how emerging approaches and new approaches are integrated into the IRIS and PPRTV methodology. She suggested that screening values potentially could be used to incorporate the new methods and develop values. She questioned how EPA laboratories interact and exchange information about emerging issues, such as early upstream effects, background additivity, and mixed modes of action, ultimately to incorporate them into the chemical assessments. A participant from EPA explained that the laboratories are co-located in North Carolina, and many of the NCEA researchers have existing professional contacts within industry or academia. He mentioned the case of neurotoxicity, in which bench scientists spoke in a forum to evaluate and interpret the data and to identify sensitive endpoints for the assessments. He mentioned that early childhood exposure assessments result from strengths inside and outside of the Agency through professional contacts and workshops. Moreover, NCEA collaborates with the National Academies on workshops focused on pivotal issues. The Center currently is organizing a workshop to discuss mouse liver tumor data. These workshops gather experts to discuss the issues that affect assessments. When issues are brought to the attention of the program, they also can be developed into charge questions for peer-review panels. Dr. Preuss added that techniques, such as PBPK modeling, involve staff members throughout ORD during the development phase and throughout the assessment process. In addition, NCEA relies on a statistics group for guidance and the National Center for Computational Toxicology (NCCT) is working to assist NCEA with the incorporation of upstream data into assessments.

Dr. Daston stated that the IRIS Program is deliberate in its rate of incorporating new methodology, such as consensus tools and BMD. From the perspective of a bench scientist, the Agency's rate may seem slow, but risk managers and decision-makers likely appreciate that the process is not implemented until it has matured. He asked how the program looks ahead to emerging technologies to begin incorporating methods when the methods still are cutting edge. Dr. Kadry explained that this will be described further during the LTG 2 presentation on Day 2. He noted that it is not a passive process.

Dr. Preuss added that NCEA staff members develop new methods to answer questions that existing methodologies could not address. Often, existing methodologies are sufficient for IRIS use, but NCEA also may request assistance from the National Academies. Specifically, a National Academies committee currently is working to identify existing methods that are being overlooked in the assessment process and methods that will be available in the near future or in the long term. Dr. Preuss estimated that the report from that committee should be available during the next year. Dr. Kadry added that methods are chosen after an internal consultation with EPA laboratories; this ensures that the assessments are current with the state of the science.

Dr. Zeise asked about the status of the peer-review process. She commented that in some cases, the analyses are very complex and might preclude adequate peer review. Dr. Preuss answered that the program has three methods by which to organize a peer review. It can request that it be conducted by one of the National Academies or the EPA SAB or the program can constitute its own panel. When using the third method, under FACA, contractors must be used to coordinate panels. He agreed that it is troubling to guarantee that sufficient expertise and familiarity with the process is ensured during peer reviews of the most complex assessments, such as PBPK. This is one advantage of using EPA staff or the SAB for the panels. He remarked that the ideal solution to organizing peer-review panels still is elusive. He added that the ISA process of including peer reviewers, experts, and interested parties at multiple steps seems appealing and might be applied to the IRIS process.

Dr. Corley noted that the program arguably includes the largest PBPK group in the nation. He cautioned that it raises a dilemma for peer review because the experts qualified for the review instead are connected with the work. He added that the same issue might arise as the computational toxicology team grows. Dr. Corley commended the program for its transformation of the field of risk assessment. He noted that the database, uncertainty analyses, and characterizations variability all are valuable to the field.

Program Office Perspectives

Ms. Elizabeth Southerland, Office of Superfund Remediation and Technology Innovation (OSRTI), OSWER, EPA
Ms. Lydia Wegman, Office of Air Quality Planning and Standards (OAQPS), OAR, EPA

Superfund Program Perspective

Ms. Elizabeth Southerland, Director of the Assessment and Remediation Division, explained that when a state suggests a waste site for remediation, OSRTI conducts a ranking of the site based on various human health and ecological risk pathways. It must score a 28.5 or higher to be denoted a Superfund site on the National Priorities List (NPL). After a site is listed as a Superfund site, a series of events are initiated. The remedial investigation/feasibility study (RI/FS) process occurs first, in which OSRTI obtains information about the site; this information may be combined with basic monitoring data gathered by the state before the site was placed on the NPL. Next, OSRTI sets a preliminary remediation goal around which it designs a monitoring plan. This is accomplished by identifying contaminants of concern. For example, if the emerging contaminant perchlorate is detected at a site, the remediation goal is 24 ppb unless state regulations require a different standard. Second, OSTRI works with ORD and NCEA to develop a baseline risk assessment. At that point, detailed monitoring commences, and the remediation goal may be refined. Next, a capability study is conducted during which different clean-up alternatives are assessed for effectiveness and cost, and the best strategy is chosen. Throughout the process, NCEA ensures that the Superfund staff members are informed about the most recent science so that they can better understand the risks and select the most appropriate remediation option.

Proposed Hierarchy for Toxicity Values

OSRTI Directive 9285.7-53 identifies a hierarchy of sources of toxicity information for use in Superfund risk assessments. Tier 1 of the hierarchy is IRIS values. If IRIS values are not available, PPRTVs are used (Tier 2). Other toxicity values that are peer-reviewed, transparent, and publicly available, such as the Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Levels (MRLs), California EPA toxicity values, or the Health Effects Assessment Summary Table (HEAST) values will be used if IRIS values and PPRTVs both are unavailable (Tier 3).

Ms. Southerland stated that, during the past 2 years, the Environmental Council of States, which organizes an emerging contaminant workgroup with the Department of Defense (DoD), has planned to require that all members use the same tiered hierarchy. If the plan is accepted by vote, it will be the first time that these standards transcended EPA programs to the level of DoD and the states.

NCEA Support of the Superfund Program

NCEA's Technical Support Center provides consultation on the use of toxicity values and may conduct special analyses upon request. NCEA supports the program through the development of IRIS values and in the development of PPRTVs when IRIS values are not available. In addition, NCEA offers chemical-specific support (e.g., uncertainty analysis associated with the development of asbestos toxicity values) as needed.

Ms. Southerland noted that NCEA expertise is particularly valuable in the development of Superfund risk assessment guidance (e.g., dermal, inhalation).

NCEA provides support for Superfund sites contaminated with lead, of which there are more than 255 on the NPL. NCEA has developed the integrated exposure uptake biokinetic (IEUBK) model for lead, which is typically used to develop cleanup levels. At a National Academies review 2 years ago, the IEUBK model was deemed the most cutting-edge modeling technique for this purpose. NCEA also provides technical peer-reviewed reports of value in conducting ecological risk assessments.

Office of Air Quality Planning and Standards (OAQPS) Perspective

Ms. Wegman is the Director of the Health and Environmental Impacts Division of OAR's OAQPS. Her division focuses on policy, using ambient air quality standards and residual risk assessments from NCEA. She noted that staff members in her division conduct cost-benefit analyses for the Air Quality Program and NCEA also provides support for these efforts.

HHRA Activities and Assessments Used by OAQPS

The NCEA activities that provide essential support for OAQPS work include: (1) generation of the ISAs, which support NAAQS standard setting; (2) generation of IRIS assessments, which support Residual Risk standard setting; (3) provision of expert advice on risk assessment methods, models, and approaches, which support OAQPS assessment and rulemaking efforts in both the criteria pollutant and air toxics programs and the mobile source air toxics rulemakings. NCEA's work is critical to EPA because it ensures the integrity, credibility, and defensibility of rules and other work products, and the timely delivery of NCEA products is central to the Agency's ability to meet statutory requirements under the CAA.

Ms. Wegman commented that the integrity, credibility, and defensibility of NCEA's documents and has earned the Center respect worldwide. She stated that timely delivery of NCEA products is crucial to her division, which is working through new NAAQS processes to try to deliver a standard every 5 years.

The CAA requires EPA to set NAAQS for six criteria pollutants—ozone, PM, carbon monoxide, lead, nitrogen dioxide, and sulfur dioxide—to protect public health and welfare. EPA must review the scientific information and the standards for each criteria pollutant every 5 years. OAQPS's partnership with NCEA is critical to the NAAQS review process. By analyzing and synthesizing the results of new studies, the ISAs inform OAQPS' understanding and interpretation of the scientific evidence. ISAs also provide inputs into the quantitative risk and exposure assessments conducted by OAQPS. ORD and OAR have been working together to improve the NAAQS review process—meeting the 5-year deadlines requires close collaboration between OAQPS and NCEA through the review cycle. Because the ISA is the core component of the review, it is essential that NCEA has the resources to complete it in a timely manner. Ms. Wegman remarked that the AQCDs have been replaced with the ISAs because the new process required an interpretation of the science in a concise document. This change should benefit the diverse audiences that rely on ISAs.

Ms. Wegman noted that the 11 people in her division have worked closely with Dr. Cote and other NCEA staff members on the NAAQS. She noted that NCEA provides support throughout the risk and exposure assessment, including the development of the scope and integrated science plans, offers continuous advice regarding existing information that should be incorporated into the assessments, and conducts reviews. During the rulemaking phase, NCEA provides support in responding to public comments, reviewing new studies that are submitted by the public, and determining if new information changes the rulemaking process. NCEA's support for NAAQS is crucial.

HHRA activities and assessments also are used by OAQPS to support the Residual Risk program. The Residual Risk program is the Agency's primary risk-based program to specifically address emissions of air toxics from stationary sources. HHRA's IRIS database is the primary source of health information for the risk assessments that support the Residual Risk program. Ms. Wegman explained that OAQPS performs exposure and risk assessments for each source category covered by the Residual Risk program. The program includes more than 150 source categories and each source category emits one or more toxic chemicals. Both chronic and acute health risks are included in the assessments. The risk assessments are based on dose-response values, mainly from IRIS. OAQPS is committed to using the best available scientific information for its risk assessments, and IRIS is OAQPS' preferred source. Ms. Wegman stated that she appreciates NCEA's efforts to provide information for the acute assessments, despite the restrictions imposed by OMB.

OAQPS currently plans to complete residual risk assessments on 40 to 50 source categories in the next 2 to 3 years. If achieved, this will allow OAQPS to comply with statutory requirements and the HHRA Program will provide support to allow OAQPS to meet that timeline. OAQPS staff members also work with the HHRA staff annually to identify priority pollutants to target for new assessments or reassessments.

The HHRA Program provides further support for OAQPS activities through consultation on assessment models, methods, and approaches, in part through participation in workgroups. Program staff members review and advise OAQPS on scope and methods plans, exposure and risk assessment reports, and responses to technical comments for NAAQS. For example, the HHRA Program staff provides assistance in interpretation of health effects evidence related to: (1) selection of appropriate health endpoints for NAAQS risk assessments, (2) selection of exposure-response and concentration-response relationships, and (3) addressing various issues such as choice of lag models, single versus multi-pollutant models, and single versus multi-city effect estimates. The program staff also provides support in characterizing science related to Estimation of Policy-Relevant Background, which is used in risk assessment. In addition, HHRA staff provides advice on exposure models, as well as scientific information used as inputs in exposure assessments conducted for NAAQS reviews. The program continues to be active throughout the rulemaking process.

Ms. Wegman commented that OAR requires consistency between the risk assessments and the benefits assessments. These documents use different assumptions and approaches, but OAR attempts to make the information consistent for the benefit of state and local agencies that implement the NAAQS.

Discussion

Dr. Zeise asked how emerging chemicals of potential concern were addressed before they were available on the NAAQS list. Ms. Wegman answered that she focuses on chemicals listed on the NAAQS list. She added that if an individual wanted to add to the list, he or she could petition the HHRA Program. The petition would have to discuss how the emerging chemical is an endangerment to public health and welfare and suggest that the chemical is derived from numerous and diverse sources.

Dr. Utell stated that NCEA provides assistance to the Superfund Program for risk assessment guidance relevant to inhalation. He asked if the guidance was directed toward a specific chemical. Ms. Southerland responded that the support was for generic inhalation guidance methodology. This included inhalation assessments for any chemical.

Dr. Corley asked if the rate of IRIS values, supplemented by PPRTVs, was sufficient for the purposes of the NAAQS or whether a higher rate was desirable. Ms. Southerland answered that both IRIS values and PPRTVs would be more helpful if a higher posting rate was established. When a site is designated as a Superfund site, work must commence immediately. If IRIS values or PPRTVs are not available, it is not possible to wait, and Tier 3 values must be used instead.

Dr. Corley asked how well the IRIS prioritization scheme fits with the organization of the Superfund Program. Ms. Southerland replied that she is pleased with the improvements made in the PPRTV process, but the Superfund Program continues to need PPRTVs that are not available. Ms. Wegman agreed, adding that the residual risk regulations are set at a high rate, and OAR prefers IRIS because it is widely accepted among interagency colleagues.

Dr. Corley asked where other risk assessment values, such as those from Health Canada, would be ranked. Ms. Southerland replied that those values would be ranked as Tier 3. She added that DoD and Ecosystems workgroups are preparing criteria for a ranking of Tier 3.

Dr. Daston asked if the screening-level assessments are held in lower esteem and perhaps would be classified as Tier 4 values. Ms. Southerland explained that analyses will not be conducted unless Tier 3 values or better are available. In that case, the Superfund Program would rely on public notice and criticism to refine the primary remediation goal.

Dr. Daston stated that, with PPRTV, priority is given to chemicals to which human exposure seems to be increasing. In contrast, Superfund sites deal with chemicals that are degrading or decreasing in exposure risk. He asked if chemicals common to Superfund sites would be given lower priority because of that characteristic. Dr. Preuss explained that the prioritization process accounts for the type of problem that the chemical presents. There may be a number of chemicals that are decreasing in prevalence or that have been banned but continue to contaminate Superfund sites. He emphasized that NCEA's primary mission with the assessment values is to service the Agency. Dr. Daston suggested that the prioritization scheme should be developed such that priorities are set depending on the surrounding characteristics of the chemical. Dr. Preuss responded that many other programs in the Agency focus on this type of question, but decisions have not been made at this point.

Day 1 Wrap-Up

Dr. George Daston, Subcommittee Chair

Dr. Daston suggested that the Subcommittee members meet to write individually at 8:15 a.m. on Day 2. He reiterated that the public portion of the meeting would commence at 10:00 a.m. Dr. Corley suggested that the Subcommittee members discuss their writing assignments one-on-one before adjourning for the day. Dr. Daston agreed and recessed the public meeting at 4:10 p.m.

The Subcommittee members segregated into groups for a working session to discuss their responsibilities for writing the report and to begin drafting their respective sections.

THURSDAY, NOVEMBER 15, 2007

Review of Agenda and Day 1

Dr. George Daston, Subcommittee Chair

Dr. Daston announced that Dr. Anderson, a member of the HHRA Subcommittee, was present although he was unable to attend yesterday. Dr. Anderson is the Chief Medical Officer for Environmental and Occupational Health at the Wisconsin Division of Health.

Dr. Daston stated that the Subcommittee members would receive information about LTG 2, partnerships and collaborations, and an analysis of IRIS users. He reminded the Subcommittee members that time was set aside on the agenda for public comment. At 12:15 p.m., Ms. Foellmer will call for public comment, and the comment session will end at 12:30 p.m.

Overview of LTG 2: Methods, Models, and Guidance

Mr. David Bussard, NCEA, ORD, EPA

Mr. David Bussard is the Director of the NCEA-Washington Division. Mr. Bussard stated that his presentation would include a discussion of the relevance and overarching goals for LTG 2, the program design and recent accomplishments, the Subcommittee's broad charge questions, and the charge questions specific to LTG 2—models, methods, and guidance.

Relevance and Overarching Goals

The primary goal of the HHRA Program is to ensure timely, high-quality chemical risk assessments and LTG 2 provides the tools, methods, and databases most needed for these risk assessments. The secondary goal of LTG 2 is to support the risk assessment community more broadly. This may include the development of tools or guidance such as characterization of exposure factors to be used across EPA program offices and regions.

These goals are used to guide NCEA in the selection of priority projects and target sufficient resources. Efforts are centered on those aspects of the risk assessment process that address exposure and dose, internal dose, hazard, dose response and health impacts. The risk assessors, particularly chemical assessors at EPA, must be supported, staff members must be informed of developments in the science that are ready for use in assessments and risk characterizations. Under LTG 2 the program matches up these advances in science and priority needs for improved risk assessments.

Program Design and Recent Accomplishments

Mr. Bussard reviewed how the work on methods under HHRA are guided by the priority needs of those doing hazard and dose-response assessments or by those doing risk assessment generally for EPA and state decision-making on environmental issues. He used recent outputs as examples. One area for methods and tools development has been tools for estimating human exposure from environmental sources. Some examples of past products supporting this need include: the *Exposure Factors Handbook*, *Child-Specific Exposure Factors Handbook*, *Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants*, and *All-Ages Lead Model (AALM) Version 1.05*. The government users of these tools most often are risk assessors in EPA and state programs. Those doing human hazard and dose-response assessments need tools for three areas: (1) estimating internal dose through the use of PBPK modeling, (2) guidance on recurring issues in hazard assessment, and (3) tools for quantitative dose-response assessment. Examples of products on the use of PBPK modeling and other dosimetry work included the *RfC Methodology*, *Approaches for the Application of Physiologically-Based Pharmacokinetic (PBPK) Models for Supporting Data in Risk Assessment*, and an International Workshop on Uncertainty and Variability in PBPK held in 2006. Examples of guidance on recurring issues with hazard characterization included EPA's *Guidelines for Carcinogen Risk Assessment* and the *Children's Supplemental Guidance* and a Summary of the NCEA Colloquium on Current Use and Future Needs of Genomics in Ecological and Human Health Risk Assessment. Examples of tools to help with quantitative dose-response analysis included updates of BMD modeling software to allow for analysis of endpoints with continuous data and development of CatReg models for analysis of endpoints across multiple domains for toxicity (e.g., functional observational data for neurological function). Finally, there also are a range of questions that arise as to how to characterize the uncertainties in estimates or how to well-characterize potential sensitivities of particular populations. Examples of tools to assist with this included *A Framework for Assessing Health Risk of Environmental Exposures to Children, Aging and Toxic Response: Issue Relevant to Risk Assessment*, and *Use of Physiologically-Based Pharmacokinetic (PBPK) Models to Quantify the Impact of Human Age and Interindividual Differences in Physiology and Biochemistry Pertinent to Risk.*

Mr. Bussard presented a list of the most frequently downloaded LTG 2 products January-August 2007. He pointed out that there had been 5,000 downloads of the *Guidelines for Exposure Assessment* and added that the *Child-Specific Exposure Factors Handbook* was downloaded numerous times, and it is not even in its final version. The large number of downloads suggests that people outside of EPA use the risk assessment documents. Mr. Bussard noted that NCEA will need to stay abreast of the increasing level of understanding and advances in computational sciences, biochemical and biological mechanisms, and the information that can be gleaned from these technologies to further the science of risk assessment.

Changing Emphases for Risk Characterizations

Mr. Bussard talked about emphasis on characterizing risk in order to better inform decision-makers and presented an excerpt from the Safe Drinking Water Act (SDWA) Amendments to illustrate these requirements. "The Administrator shall…specify to the extent practicable: (i) each population addresses by any estimate of public health effects; (ii) the expected risk or central estimate of risk for the specific populations; (iii) each appropriate upper-bound or lower-bound estimate of risk; (iv) each significant uncertainty identified in the process of the assessment of public health effects and studies that would assist in resolving the uncertainty…" Mr. Bussard stressed three points about this section of the SDWA Amendments: transparency about the impacts of the choices made, not just upper-end estimates, and differing populations.

Under LTG 2, the program's efforts are targeted on areas that critically affect assessment, new science ready for consideration, changing emphases in characterization objectives, and critical mass. Ongoing efforts address, in particular, work in the areas of susceptible populations and sources of variability as well as estimations of expected values and quantifying uncertainty.

Quality

Strategies for maintaining quality and achieving these goals include: (1) maintaining an experienced expert staff and training of post-docs and new staff, (2) building of cross-discipline NCEA work teams, (3) collaborations with ORD colleagues and external experts, (4) development of case studies to test hypotheses and (5) sponsoring workshops and forums on scientific issues.

Currently, NCEA has an experienced, expert staff and recently has hired expert post-doctoral fellows. In addition, NCEA has set-up cross-discipline work teams in the areas of biology (MOA and PBPK), quantitative experts (statistical modeling), and users support (exposure factors handbook).. In addition, NCEA staff members have organized and sponsored numerous forums and workshops.

There are various review levels at NCEA. Work prepared under LTG 2 includes peer consultations and involvement both internally and externally. Methodologies undergo extensive peer review and public comment. Mr. Bussard reiterated that the National Academies currently is preparing a report of new and emerging methods for ORD implementation.

Leadership

NCEA has developed highly significant guidelines that are widely used within and outside EPA. In addition, NCEA staff members actively participate in the risk assessment community—as members of work groups and committees. Mr. Bussard referred the Subcommittee members to Poster #13 for more information.

Coordination and Communication

Coordination and communication is strong at NCEA particularly because many of the staff members involved in methods development also prepare assessments or work very closely to users both within the HHRA Program as well as the program offices and regions. In addition, external groups and collaborators are consulted frequently. Once methods are available, they are disseminated via Web sites, journal article publications, and EPA reports. Many NCEA staff members are co-authors on MYPs for other ORD programs; this is emblematic of the extensive interaction throughout ORD.

Mr. Bussard described some examples of collaborations with ORD. Program staff work with ORD's National Center for Environmental Research (NCER) on Requests for Applications (RFAs) and with the other laboratories to identify priority research needs. HHRA Program staff members participate in the ORD PBPK workgroup and on many projects with other ORD laboratories and centers such as the report on Approaches for the Application of Physiologically-Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment. Staff members have participated in workshops on uncertainty in PBPK and good practices. In addition, they have assisted with development of a database on physiological parameter and have collaborated on modeling for specific chemicals. NCEA has collaborated with others in ORD on disinfection by-products research and analysis and the program staff works on research planning and coordination teams for other MYPs.

Outcome: Success

Success for LTG 2 is determined by the quality and usefulness of the LTG 1 and LTG 3 assessments. The models, methods, and guidance from LTG 2 contribute to the quality and usefulness of EPA risk assessments and the world-wide use of these products.

Charge Elements Specific to LTG 2

With respect to appropriateness, Mr. Bussard stated that it would be very difficult to do quality risk assessments without the products from LTG 2. Many of the topic areas or projects that are being addressed under LTG 2, arose out of data gaps or uncertainties cited in individual assessments. To ensure quality of the products, the program established excellent peer review and revision processes. The models, methods, and guidance from LTG 2 are used by IRIS staff, other EPA staff, and those outside of EPA; this is evidenced by the LTG 1 presentation and the many downloads and users of LTG 2 products.

Mr. Bussard noted that the Subcommittee was asked to assess whether LTG 2 products enhance scientific quality and objectivity, characterization of risk and uncertainty, and quantitative analysis of uncertainty. There are several areas in which work being conducted under LTG 2 is addressing quantitative analysis of uncertainty. For example the *Exposure Factors Handbook* provides percentiles, rather than values, of human activities. This allows users to characterize variability in a population that might lead to activity-based variabilities in exposure. Another area is the PBPK model for quantitative risk assessment, where the uncertainty around each value or within each model is presented to users.

NCEA also is working to develop integrated frameworks to capture and discuss uncertainty. The Center has commissioned a number of white papers that should be published in the next year. In addition, NCEA staff members are involved in two Resources for the Future seminars to discuss integrated frameworks and learn the limitations and strengths of each framework.

Posters

Mr. Bussard stated that the posters for LTG 2 are organized in roughly similar order to the slides on how priorities guided past accomplishments. The posters illustrate some of the program's recent or current work and directions for the future. He then reviewed a list of the poster presentations for LTG 2.

Approaches for Assessing Environmental Exposures
#1: Improving Chemical Risk Assessment with Better Exposure Assessments

Internal Dose and PBPK Modeling
#2: Chronic RfC and Exposure-Response Methodologies in Revision and Under Development
#3: Advancing the Development, Evaluation, and Use of Physiologically-Based Pharmacokinetic (PBPK) Models in Risk Assessment

Hazard Characterization (and Dose Response)
#6: Use of Mode of Action Data to Inform Human Health Risk Assessment
#9: Whole Mixture Methods for Assessing Health Risks from Exposure to Chemical Mixtures
#10: Component-Based Health Risk Assessment methods for Chemical Mixtures

Dose-Response Analysis
#7: Use of Biologically-Based Dose Response Models
#8: Dose-Response Modeling at EPA: Research and Development

Risk Characterization (and cross-cutting issues)
#4: Utilizing Early Life-stage Data in Risk Assessment
#5: Characterization of Environmental Risks to Older Adults
#11: Evaluation of Uncertainty, Data Derived Uncertainty Factors, and Variability

Other
#12: Approaches To Address Emerging Issues in Risk Assessment

#13: Leadership, Collaboration, and Promotion in the Development and Use of Risk Assessment Models, Methods, Databases, and Guidance

Mr. Bussard noted that the posters provide discussions about MOA, which can be used in qualitative judgments, quantitative work, and methods work. He also pointed out that the posters address the challenges associated with mixtures and how NCEA approaches assessments and dose response analyses involving mixtures. Finally, each poster discusses uncertainty analysis to some degree, and Poster #11, "Evaluation of Uncertainty, Data Derived Uncertainty Factors, and Variability," focuses entirely on the subject of uncertainty.

Discussion

Dr. Corley complimented the workgroup involved in methods development and in variability and uncertainty analyses. He commented that it would be useful for the workshops to be developed into white papers discussing how to incorporate the models. He asked how the methods development applies to PPRTVs for which there are less data for prioritizing and screening. Mr. Bussard noted that methods for PPRTVs must be streamlined and efficient. Dr. Andrew Gillespie, EPA, mentioned that one of the posters addresses emerging methods for PPRTVs. He noted that NCEA is not conducting research to improve prioritization because the Superfund Program sets priorities for PPRTVs based on the chemicals detected at waste sites and the availability of IRIS assessments.

Referring to the National Academies' *Toxicity Testing in the 21st Century: A Vision and a Strategy* report, the recent activity in the field of genomics, the use of structure information, and the extrapolation of *in vitro* data for dose-level effect information, Dr. Zeise noted that these resources may provide insight into chemicals that are data sparse with respect to apical endpoints. She asked whether the program was integrating information from these sources. Mr. Bussard replied that chemicals are being explored through an MOA framework to determine how mechanistic information can be incorporated and to allow species-to-species extrapolation. He noted that Dr. Gillespie's group had studied structure activity and the NCCT is working extensively to determine how pesticide databases can be mined to identify patterns and validate toxicological predictions.

Dr. Daston commended the HHRA Program for making substantial achievements with a small staff and for leveraging other talent within the Agency. He remarked that, at Procter & Gamble, a "communities of practice" mechanism is used in which people in different organizations who share common expertise and interests gather on a grassroots basis. He added that the NCCT has implemented a similar mechanism and asked if NCEA had considered such an approach. Mr. Bussard affirmed that NCEA had on some occasions, and it was a useful way to share ideas, but he noted that it is difficult for workgroups to communicate broadly and sufficiently with other workgroups. He also stated that communications tend to become infrequent when a project is no longer ongoing. Dr. Daston commented that communication is well underway in the program, but it might be helpful to involve staff from program offices in other areas that share similar interests.

Dr. Daston stated that the uncertainty analyses provide a richer assessment for decision-makers, but he wondered if providing too much information would not be amenable to decision-making. Mr. Bussard agreed but said that program staff had not yet interviewed users about risk assessment information. The staff members are eager for feedback and acknowledge that with new methods of data analysis, new methods of data communication also are necessary. Dr. Preuss added that, when a risk manager is presented with a range of exposure risks, the natural tendency is to set standards based on the lowest portion of the range. To avoid this misinterpretation, NCEA is working to develop reference doses based on specific model systems and endpoints. This communication strategy is near completion for a perchloroethylene assessment. Specifically, a series of charts indicate the effects on the central nervous system as the dose of perchloroethylene is increased. Similar effects on other bodily systems will be available along with a summary assessment. This approach is an alternative to a dose response analysis.

In addition, a cancer assessment was conducted in which an extensive uncertainty analysis was provided, and the program's preferred response was indicated.

Dr. Daston asked whether the HHRA Program staff were involved formally and systematically in research planning. If not, he wondered whether there was a way to formalize the process so that staff members could contribute to the integration and interpretation of data from a variety of sources. Mr. Bussard answered that Research Coordination Teams (RCTs) exist for each of the MYPs. The RCTs track the discussion and provide input. Following an assessment, RCTs ideally could identify and meet the needs of the users, but in many cases, pressure to publish the next assessment precludes extensive followup. He pointed out that in the Human Health Research MYP, which feeds directly into broad questions of risk assessment methodology, two of its LTGs address incorporating MOA data into biologically based and quantitative modeling and understanding susceptible populations. This continuity suggests that the method is formalized. Dr. Preuss added that an NPD is assigned to each MYP, and one of the NPD's responsibilities is to ensure that ORD understands the work that is needed. This allows for communication at multiple levels.

Dr. Anderson asked about the utility of external toxicology data, particularly when the data are not peer reviewed or published. Mr. Bussard responded that the data can contribute to priority setting, and data from the chemicals may warrant full assessments.

Dr. Anderson stated that IRIS is data-rich and addresses many apical endpoints. He asked if NCEA tracks the generation of data that can be used in future IRIS assessments and why NCEA uses external data sources rather than gathering its own data experimentally. He raised the issue of a decrease in data availability, particularly for human epidemiology studies. He wondered if NCEA had considered that possibility in its strategic long-term plans. He asked if NCEA tracks publications to foresee when investigator-driven, external research will undergo a shift in methodology. Mr. Bussard replied that a number of staff members review testing protocols and paradigms for chemicals. He acknowledged that many of the epidemiological studies that NCEA uses in its assessments are observational because these studies generate a strong signal-to-noise ratio. NCEA is working, particularly with NCCT, to prioritize and focus resources to predict changes in risk assessment methodology.

Dr. Preuss stated that there often is insufficient funding for assessment-based work. The National Institutes of Health and the National Science Foundation tend not to support work on exposure assessments or PBPK modeling. Approximately 10 years ago, the National Center for Environmental Research (NCER) was created, and $100 million was moved from ORD's research budget to support the NCER extramural program. Because of budget cuts, NCER's funding has decreased. Currently, industry seems to be the primary resource for assessment data.

Poster Session: LTG 2

The Subcommittee members reviewed 13 posters in the LTG 2 Poster Session. During the 90-minute poster session, each Subcommittee member had the opportunity to ask questions about the research or clarify specific points with the EPA presenter(s). Poster abstracts and a book of poster reproductions were provided to Subcommittee members before the meeting.

Public Comment

Dr. Daston explained that four members of the public had submitted advance requests for comment. One of them was present at the meeting, two were present via teleconference, and a third communicated her comment via e-mail. Dr. Daston asked if there were additional requests for comment; there were none. He reiterated that each comment was limited to 3 minutes.

Dr. Daston summarized the comment sent by e-mail. It was submitted by Ms. B. Sachau. She stated that she perceived public health to be declining while taxes are increasing. She expressed concern about food safety and illegal immigrants using tax dollars at the expense of services to American citizens. Dr. Daston stated that there are printed copies available of the e-mail. He added that the Subcommittee members do not need to respond formally to the comments.

Dr. John Dunn, who practices emergency medicine in Fort Hood, Texas, provided the second comment. He has been an emergency physician since 1974 and a lawyer since 1979. He stated that many of the studies conducted by EPA are small effects studies, that is, studies with a relative risk less than two. Large projections are made from these studies. This issue of high-dose toxicology combined with linear modeling presents uncertainty problems that EPA and the Subcommittee members should address. Dr. Dunn cited a reference manual that explains which types of scientific evidence should be admissible in a federal court. He stated that the chapters on toxicology and epidemiology in the manual were written by esteemed experts, and both recommend against small effects studies. He stated that, as an emergency physician, he personally knows that thresholds make a difference in human health effects. He agrees that EPA's Air Quality Program is successful, but he noted that there are no studies that indicate the work products of the program are responsible for this success. He recommended that EPA identify the benefits of its programs during the past 30 years. Dr. Preuss had stated that there should be increased funding for the chemical and genomic studies being conducted currently; Dr. Dunn explained that he disagrees because of the amount of uncertainty inherent to these methods. Moreover, the public believes that the air quality is worse and that chemicals in the air are fatal. Indeed, there are serious toxicities that need to be removed, but he hopes that EPA and the Subcommittee will address these issues rationally and not worry about the continuance of funding.

Dr. Stan Young gave his comments via teleconference. He is the Assistant Director for Statistics at the National Institute of Statistical Sciences. He stated that data should be publicly available, and evidence should not be admissible otherwise. The National Academies panels study these issues, and Congress has acknowledged that data are being used to make regulatory decisions. Therefore, it is fair for data to be available. In the medical sciences, 80 percent of claims derived from epidemiological studies have failed to be repeatable. EPA should be aware of this and should scrutinize the statistics used in the epidemiological studies from which it composes risk assessments.

In randomized clinical trials, people are assigned to treatment groups at random. In this way, groups are originally equivalent, and if the treatment has an effect, the groups will be different at the end of the trial. In contrast, in observational studies, groups initially are different and by statistically adjusting each group with covariates, the groups may be brought into alignment. Unfortunately, if covariates exist that are real but not measured or known, they can vary with the statistical adjustment. Dr. Young had submitted to the Subcommittee a graph of the United States showing the deaths as a result of ozone. He pointed out that the death rate is elevated in New York and New Jersey, but the rest of the country has a uniformly low rate. He stated that it is unfair to regulate ozone across the United States when the measured effect is in one location.

Dr. James Enstrom provided his comments via teleconference. For 30 years, he has conducted peer reviews and epidemiological research, and he has been a faculty member of the University of California at Los Angeles since 1976. He has been a member of the American College of Epidemiology since 1981, and President of the Scientific Integrity Institute since 2005. In 2005, he published a detailed analysis of the relationship between fine particulate air pollution and mortality from 1973 to 2002 in a California Cancer Surveillance Program (CPS) 1 cohort. He found no relationship between $PM_{2.5}$ and mortality from 1983 to 2002, and he demonstrated that his results were consistent with the results from the 1982 to 1989 CPS 2 cohort for California. Unfortunately, his results have not received proper consideration from EPA. This year, he also submitted a detailed analysis of the relationship of all major air pollutants and mortality for the California CPS 1 cohort from 1960–2002. Two major U.S. journals that publish many air pollution epidemiology papers narrowly rejected his manuscript after giving it little or no peer review; these

journals refused to objectively consider the largest, longest, and most comprehensive analysis on air pollution ever conducted on a California population. Their rejection and additional evidence indicates that there is a publication bias against findings from independent investigators. Air quality standards must be based on all available epidemiology evidence, and evidence should be available for independent analysis, particularly for research funded by EPA and other federal agencies. In the spirit of the Data Quality Act, Dr. Enstrom is willing to facilitate independent analysis of his California CPS 1 data, and he proposes that the Subcommittee meet with experienced epidemiologists to discuss and debate the air pollution evidence in the United States. Diverse points of view should be represented on the panel. In the interest of sound air quality regulations that impact all Americans, EPA should give fair consideration to legitimate studies.

Dr. Daston thanked the members of the public for their comments. He stated that the Subcommittee members would consider the comments during their deliberations.

At the request of the Subcommittee members, the EPA presenters returned to their posters for 15 minutes during the lunch break so that the Subcommittee members could ask additional questions.

Poster Session Discussion and Questions on LTG 2

HHRA Subcommittee

Mr. Allen asked about research efforts that seem to be transitioning to risk assessment methods. He wondered how NCEA staff members determine that a method is ready for incorporation into an assessment. Mr. Bussard responded that NCEA may take a case study approach, but it would need to be careful not to oversimplify the case. In important complex assessments, in which existing methodology is not useful, new methods can be tested. Mr. Allen asked how NCEA staff members choose to evaluate compounds of concern that require additional resources instead of conducting routine assessments, given the pressure to produce assessments at a high rate. Mr. Bussard explained that the staff must use scientific judgment.

Dr. Utell commended the program staff on a comprehensive and interesting poster session. He stated that his question was answered during the poster session, but he raised it again for entry into the public record. He was interested particularly in the slide regarding "science opportunities." He asked how NCEA allocates resources along a timeline. Mr. Bussard answered that NCEA maintains a portfolio of both solid and risky investments. He stated that a single methodology cannot give information for every chemical assessment, but incorporating new methods requires a learning curve before it is obvious that a method will be useful.

Dr. Utell stated that, during the poster session, he asked the same question of an EPA staff member. The participant repeated his answer for the public record. He stated that, in the case of an enzyme responsible for the metabolism of an environmentally important contaminant, it would seem that any change in the nucleotide sequence of the gene coding for the enzyme automatically confers either resistance or susceptibility to the cell. In fact, that may not be true. Often, single nucleotide polymorphisms (SNPs) are identified from screens and not mapped to the sequence. The polymorphism may be in an intron or may involve a functional change in the protein, but for a change in enzyme activity, it would be necessary for the amino acid sequence to be altered. Even then, the amino acid change may not affect protein folding or the enzyme active site. Enzyme kinetics can be performed to characterize a SNP in terms of metabolic rate constants. When the constants are known, they can be extrapolated to an impact estimate on an intact body.

Dr. Daston confirmed that there were no other comments. He stated that members of the EPA regions would provide their perspectives. Ms. Kathy Callahan would speak first; Mr. Kerrigan Clough would speak second. Dr. Preuss stated that Ms. Callahan and Mr. Clough are senior Deputy Regional Administrators (DRAs) and direct the functioning of their regions.

Regional Perspective

Ms. Kathy Callahan, DRA, EPA Region 2; and Mr. Kerrigan Clough, DRA, EPA Region 8

Region 2 Perspective

Ms. Callahan explained that she is not a scientist, but is responsible for directing the work conducted by EPA Region 2, which includes New York, New Jersey, the commonwealth of Puerto Rico, and the territory of the U.S. Virgin Islands. She has worked for this region for 36 years on implementation programs. During the past 10 years, she has become more engaged in the issues of science and risk. She stated that NCEA's HHRA Program has continually engaged Region 2; she added that other ORD staff members also have provided substantial support.

IRIS Used for Regional Risk Assessments

Ms. Callahan stated that assessing risk at facilities is challenging. IRIS provides a solid peer-review basis for toxicology values, and it is the foundation of the risk assessments conducted by regional staff. In the region, most of the risk assessors are associated with the Superfund Program. There also are risk assessors with expertise in human health and ecology, and they address issues that emerge from the environmental assessment review under the National Environmental Policy Act. In this role, the staff members implement remediation efforts as part of the permitting process.

IRIS also is used as a resource when states require scientific guidance in their risk judgments. The states may have multiple regulatory programs, and it is challenging to apply consensus toxicity values, particularly when new chemicals emerge. The states and regions also appreciate IRIS because they can contribute to the chemical nomination process.

Support for World Trade Center Response

During the World Trade Center (WTC) response, an analysis was conducted on the toxicological effects of PM from dust resulting from the building collapse. The study collected 2.5 μm particle samples from WTC dust and compared those to reference samples that were well characterized with respect to chemistry and pulmonary toxicology in rodents. The study determined that the samples were alkaline, calcium based, and were attributed to crushed building materials. In addition, there were asbestos concerns associated with the dust.

The region conducted immediate clean-up activities, but the dust continued to be a concern because it was on the exteriors and in the interiors of nearby buildings. NCEA developed a long-term plan to determine whether residents might be re-exposed to dust that was entrained in heating and ventilation systems. Variables such as the degree of physical isolation and the distance from the collapse site added uncertainty to the efforts, but the analyses were continued. Dust residuals around the city and aspects of resulting fires were analyzed. Specifically, internal patterns of dioxin forms were compared to determine a signature associated with the WTC fire event. Unfortunately, the data set was not sufficient to discriminate the WTC fire from other fire sources.

EPA, the New York City Department of Health and Mental Hygiene, and ATSDR conducted a small sample study to collect information about potential exposures in October and early November of 2001. Respiratory effects of the WTC collapse were examined. Various pollutants to which the community may have been exposed, such as PM, metals, polychlorinated biphenyls, polycyclic aromatic hydrocarbons, dioxin-like compounds, asbestos, silica, synthetic vitreous fibers, and volatile organic compounds were evaluated in the inhalation pathway. Trends emerged in the air monitoring data associated with location, time, and concentration. The evaluation concluded that, with the exception of those exposed immediately

following the collapse and perhaps during the next few days, people in the surrounding community were not likely to suffer from serious long- or short-term health effects.

ORD and NCEA staff members have worked closely with the region, particularly on a WTC Expert Panel. The panel met for 18 months, during which it identified unmet public health needs and recommended steps to minimize risks.

The region presented its data and organized a peer review of its cleanup program. Specifically, the region proposed to use asbestos as an indicator chemical for other contaminants. The result of the review was that asbestos was a reasonably good choice, but it should be combined with lead.

Ms. Callahan pointed out that New York City has high levels of lead and has never met the NAAQS. Because of these existing contaminants, it was challenging to identify chemicals that emerged or increased in concentration following the collapse of the WTC. The WTC efforts have continued for 6 years. They have resulted in close working relationships and mutually beneficial collaborations.

NCEA Support for Data Analysis

Ms. Callahan stated that funding is allocated annually for projects of interest to the region. One of the current projects aims to obtain more information about mercury levels in fish and shellfish in the New York City fish markets. The New York City Department of Health and Mental Hygiene performed a biomonitoring study of the population and found that blood mercury concentrations were elevated above the national average among participants of Asian extraction. The region worked with the U.S. Food and Drug Administration to provide a statistically representative basis for a fish tissue evaluation. Data analysis will be coordinated through NCEA. Ms. Callahan stated that fish consumption is a controversial topic, and the region is excited to contribute to a cutting-edge knowledge base; this would not be possible without the expertise of NCEA staff members.

Region 8 Perspective

Mr. Clough explained that Region 8 encompasses Colorado, Utah, Montana, Wyoming, North Dakota, South Dakota, and 27 tribal nations.

He remarked that, when human health studies questioned whether the regions were following the proper protocols, Dr. Preuss, Director of NCEA, met with the Deputy Regional Administrators from each region to discuss protocol choice and the types of human health studies the regions should conduct. Mr. Clough thanked Dr. Preuss for his assistance with this matter.

Mr. Clough stated that the Libby, Montana, asbestos site is one of the most important Superfund sites in the country. The asbestos exposures have contributed to 300 fatalities, and 700 residents are extremely ill as a result of contamination. Libby has a few thousand residents. For years, a mining company allowed employees to use asbestos-contaminated insulation materials in their homes. Clean-up efforts have been in place for 7 years, and a few hundred homes have been cleaned. Residents are monitored each year.

NCEA and other ORD laboratories worked with other agencies to develop a suite of 16 studies to test the effectiveness of the remediation efforts at Libby. The studies have been funded by NCEA, ORD, and OSWER, and four of the studies are led directly by NCEA staff members. The studies include cancer assessments and epidemiological experiments. The projects are being led by senior managers from ORD, OSWER, and Region 8. The objective is to identify persistent health issues and support the health needs of the community.

Discussion

Dr. Zeise asked how the regions would utilize an additional $2 million of NCEA funding. Mr. Clough answered that high-priority data gaps remain, and a comprehensive asbestos model would be useful. He would recommend that ORD and NCEA establish a longer term asbestos research program to continue the effort and to extend research to other potentially dangerous forms of asbestos. Ideally, the different forms of asbestos could be assessed simultaneously as that approach would save time and effort and be cost effective. Ms. Callahan stated that there is a clear scientific consensus that there are major questions with regard to toxicity and asbestos that remain unregulated. Regarding Region 2, additional funding could be allocated to studies on localized watershed quality. The Regional Applied Research Effort (RARE) is relied on for expert advice when IRIS values are not available, but RARE-derived values are not held to the same peer-review standards as IRIS. For this reason, it would be important to invest additional funding in the IRIS effort. Ms. Callahan noted that Region 2 suggests projects annually for which there has been insufficient funding. She offered to provide a list of the projects.

Dr. Corley asked whether 16 annual IRIS assessments and 50 annual PPRTVs would be a sufficient rate to meet the regions' needs. Ms. Callahan responded that it would still be a challenge, because clean-up efforts include a multitude of potential chemical exposures; many of these chemicals are not available in the IRIS database. Dr. Corley asked whether an improved prioritization strategy or an increased rate of assessments would be preferable. Ms. Callahan answered that more assessments would be preferable.

Mr. Allen requested more information about ongoing asbestos-related activities. Dr. Preuss answered that the Libby site is being evaluated for cancer and noncancer effects. In addition, medical surveillance is being conducted to understand the impacts of the asbestos contamination. Moreover, asbestos-related epidemiological data are being integrated with clinical data.

Dr. Preuss explained that ORD contributes to all of the work that NCEA conducts. He emphasized that crises cannot be predicted but require immediate response by NCEA staff members. In the case of Hurricane Katrina, Mr. Bussard led the toxicology studies. This required a priority shift away from the work in which Mr. Bussard was involved before the crisis.

Dr. Daston remarked that NCEA staff members devote significant time to incidence response. He wondered if the work could be accounted for in the MYP. Dr. Preuss answered that he was not sure how emergency response would be captured in the MYP. Perhaps he could assign an emergency fund, but the unexpected nature and magnitude of the events makes it difficult to set aside funding in advance. Dr. Daston explained that he encounters unexpected issues at Procter & Gamble, and he may be able to suggest a solution. He proposed that Dr. Preuss estimate the percentage of time that NCEA staff members are involved in emergency response.

Mr. Clough commented that the asbestos issue is not localized to Libby, Montana. There are many sites throughout the United States to which asbestos-contaminated materials are shipped. To enact a successful cleanup, all of the asbestos sites must be considered and comparisons of the sites may be necessary. Moreover, the states set values for contaminants that may not be consistent with IRIS assessments, yet state standards mandate the clean-up efforts. This can pose a problem for effective and widespread clean up.

Dr. Utell stated that NCEA contributes extensive effort to unscheduled events; it would seem that the Annual Performance Goals (APGs) do not acknowledge those efforts. Dr. Preuss agreed. Dr. Utell asked why the effort was not incorporated into performance evaluations. Dr. Preuss responded that the crises are unexpected at first; however, once they become a consistent issue, they are incorporated into NCEA's long-term plans. For instance, the Libby asbestos situation now is listed as an IRIS project. He remarked that full coverage of all NCEA activities was not necessary in prior OMB reviews because the examiner only evaluated key outputs: IRIS assessments and ISAs.

Dr. Anderson stated that the regions monitor the environment and may be able to detect some crises in advance. He asked if NCEA staff members meet to think strategically about issues that may become crises in the future. He also wondered how these crises impact the IRIS Program when staff members must shift their priorities to the crisis. Dr. Preuss answered that potential crises are discussed during research planning phases. Workshops also may be held and research efforts may be increased to assess the problem more fully. Ultimately, the contaminants may be selected for IRIS assessments.

Ms. Callahan stated that, approximately 5 years ago, Region 2 met with ORD and program offices to discuss emerging issues from a regional perspective. The meeting gave the region the opportunity to communicate with ORD and the program offices, and all parties deemed it beneficial. As a result, the region and program offices have agreed to meet bi-annually. The regions also are contributing to the Science Policy Council (SPC). Two or three DRAs typically are represented on the SPC, and when Ms. Callahan was a Council member, she had the opportunity to discuss the issues within her region and learn about related research within ORD.

Partnerships and Collaborations

Dr. Tom Burke, Bloomberg School of Public Health, Johns Hopkins University (JHU)

Dr. Tom Burke stated that he is the Director of the Johns Hopkins University (JHU) Risk Sciences and Public Policy Institute, and he chairs an ongoing National Academies Committee on Improving Risk Analysis Approaches Used by the U.S. EPA. He has had the unique perspective of serving as a state regulator, state health official, and an academic throughout his career. He stated that NCEA has contributed substantially to the science of risk assessment.

Years ago, it was determined that the nation had insufficient knowledge about risk assessment. Since that time, NCEA has been instrumental in providing tools, guidelines, and case studies. The National Academies panel is examining the breadth and challenges of NCEA, and Dr. Burke noted that the Center has been actively involved in teaching, seminars, student support, employment for graduates, research support for investigators, and guidance documents and workshops for risk assessors.

The Agency was instrumental in a project at JHU to summarize risk assessment and advance the field. Dr. Burke stated that more values are being generated and these values need to be interpreted and communicated. The project led to a definition of MOA and approaches for evaluating and classifying the evidence related to MOA. Risk assessments and risk characterizations need to consider default models, model averaging, additivity to background, background and incremental risks, and cumulative exposures. These issues should be incorporated into assessments, but it is challenging to address the tremendous population variability associated with these issues. The results of the project will be published.

Dr. Burke also chaired a working group of the Board on Environmental Studies and Toxicology. He stated that, in nearly every first session, a leader from NCEA would brief the panel, set the scientific context, and impact the thought process.

The National Academies committee that Dr. Burke chairs has been asked to develop scientific and technical recommendations for improving the risk analysis approaches used by the Agency. The committee will conduct a scientific and technical review of EPA's current risk analysis concepts and practices and will focus primarily on human health and ecological risk analysis. In making recommendations, the committee will indicate practical improvements, both short term and long term. The committee must consider: (1) the increased role for probabilistic analysis in risk analysis; (2) the scientific basis for and alternatives to default assumption choices made in areas of uncertainty; (3) quantitative characterization of uncertainty resulting from all steps in the risk analysis; (4) approaches for assessing cumulative risk resulting from multiple exposures to contaminant mixtures; (5) the involvement of multiple sources, pathways, and routes; (6) variability in receptor populations;

(7) biologically relevant MOAs for estimating dose-response relationships; (8) improvements in models of environmental transport and fate, exposure, PBPK, and dose response; (9) how the concepts and practices of ecological risk analysis can mutually inform and improve the concepts and practices of human health risk analysis; (10) the scientific basis for derivation of uncertainty factors; and (11) the use of value-of-information analyses and other techniques to identify priorities and approaches for research to obtain relevant data and increase the utility of risk analyses.

Dr. Burke noted that risk assessments have an inherent political context and economic importance that must be considered. He stated that policy decisions may be delayed by decision-makers requesting more data. Moreover, the science may be attacked because of the policy it supports. Dr. Burke cautioned that the politics of risk management are a significant driver for the demands of characterizing uncertainty.

Dr. Burke suggested that NCEA employ more senior staff, particularly because a retirement wave will occur in the near future, and funding for new researchers is important. He added that NCEA's contribution to the science is unmatched by other organizations. The Center provides a unique perspective and an in-depth understanding of the underlying laboratory research.

Discussion

Dr. Zeise asked if Dr. Burke had any suggestions regarding the political context of risk management approaches. Dr. Burke responded that some of the challenges will be addressed in the National Academies report. There are challenges inherent in the dependence on a risk assessment value. He would suggest that the Agency re-evaluate the management of risk assessment process. He noted that framing the issues around the best options for the public and environmental health is more beneficial than generating massive quantities of data to derive the best risk value. He noted that the level of risk analysis should be matched to the decision.

IRIS User Analysis: Background and Preliminary Results

Mr. Jim Solyst, Environ

Mr. Jim Solyst has been involved with the IRIS Program since 1982. He currently is in the process of analyzing IRIS users external to the Agency. His tasks have been to categorize IRIS users, to collect information from representatives of each category, and to prepare two reports: one discussing his findings and the other suggesting pilot projects.

Mr. Solyst did not conduct a survey because it would require OMB approval, and it was not appropriate for this approach. Instead, he identified categories and interviewed representatives of the categories under the premise that each individual was speaking honestly and not on behalf of his or her company. The interviews varied in length and mode (phone, face-to-face, group, or individual), but the same material was discussed in each interview.

The main categories of IRIS users were state agencies, federal agencies, academia, industry, nongovernmental organizations (NGOs), research organizations, and other countries. A more difficult challenge was developing subcategories. During the preliminary stages of his analysis, Mr. Solyst spoke with 45 non-EPA IRIS users representing the following subcategories: two federal agencies that are regulated parties; one federal agency that is not a regulated party; two state environmental regulatory agencies with toxicology resources; one state environmental regulatory agency with no toxicology resources; one state public health department that provides toxicology services to the regulatory agency; two large chemical companies; two large companies downstream to chemical production; two research organizations; two NGOs; one trade association for downstream chemical users; and one non-U.S. institution.

Mr. Solyst found that users were eager to discuss IRIS and consistently stated that the program was worthwhile. The representatives of the subcategories typically were involved in the field of toxicology or epidemiology. He found that IRIS is used by people with technical expertise. In contrast, values such as ATSDR MRLs were used to communicate with the public.

The users consistently complimented the IRIS template and the fact that IRIS defined key terms. Above all, users choose IRIS because it is a peer-reviewed, EPA consensus document. This characteristic distinguishes IRIS from every other chemical assessment. For this reason, IRIS is chosen above all other assessment values, even when the assessment is out-of-date. Although state agencies with toxicologists may supplement IRIS files with other studies, these studies never supersede an IRIS assessment.

Frequent non-EPA IRIS users generally relied on IRIS either as a chemical database or a regulatory driver. For regulation, IRIS always is considered first in the United States, and it appears that this also is true globally.

IRIS is a well known product name. Although decision-makers generally do not use IRIS, they want to know that it is part of the decision-making process. Among users, IRIS is not known as an NCEA product or an ORD product, but rather that it is an EPA database. Moreover, most users do not interact with NCEA staff members unless a chemical they nominated is being assessed.

An IRIS assessment in development is used differently than a finalized assessment. Users may offer comments or criticisms during the development phase, but once an IRIS assessment is finalized, it is accepted by its users.

The only significant criticism among users is that there are not enough IRIS assessments. This is true particularly for the controversial chemicals that state agencies and regulatory parties are encountering currently. The absence of an IRIS assessment disappoints IRIS users, and many users attribute the lack of timeliness to a lack of resources or to industry competition. Many users comment that the publication rate for assessments used to be more frequent.

In the absence of an IRIS assessment, decisions still must be made. Indeed, state regulatory agencies and chemical manufacturers will develop their own values. This requires time and resources. Moreover IRIS users often resent the need to create their own values because they must defend them continually. In contrast, IRIS values are accepted broadly. Mr. Solyst noted that IRIS users who were forced to develop their own assessments may be able to offer their expertise as a resource to the Agency.

Frequent users of IRIS have expressed interest in communicating with ORD and with each other. Such a meeting could be mutually beneficial. Mr. Solyst stated that users also would appreciate if citations were given for studies that occurred after an assessment was published.

Mr. Solyst emphasized that the data he presented were preliminary, and he planned to interview members of California EPA, academia, and the European Union for additional insight.

Discussion

Dr. Utell stated that he was surprised that Mr. Solyst did not interview regulatory attorneys. Mr. Solyst explained that he planned to interview attorneys but had not yet reached that demographic in his analysis.

Dr. Daston stated that the Subcommittee members would use the remainder of the day to work individually on the Subcommittee report. He recessed the public meeting at 3:35 p.m.

Subcommittee Working Time
HHRA Subcommittee

On Thursday afternoon, the Subcommittee members discussed details for completing their evaluation and worked individually on sections of the report.

FRIDAY, NOVEMBER 16, 2007

Subcommittee Working Time
HHRA Subcommittee

The Subcommittee members assigned to the various sections of the report used the first segment of the working session to revise their portions of the review. Subcommittee members then summarized their sections of the report, commented on the sections completed by other Subcommittee members, collaborated with their workgroups on the language and structure of their assigned sections of the report, reached consensus on areas of disagreement, and exchanged information to assist overall preparation of the Subcommittee's report.

Preliminary Report Out
Dr. George Daston, Subcommittee Chair

Dr. Daston stated that the Subcommittee was appreciative of EPA's efforts. He reiterated that the BOSC assigns a narrative term to each LTG: "Exceptional," "Exceeds Expectations," "Meets Expectations," and "Not Satisfactory."

The Subcommittee members classified LTG 1 as "Meets Expectations." A consistent number of IRIS values and PPRTVs are published, and the program is meeting its APGs while maintaining a high-quality product. This is true even as new methods are developed and outdated assessments are revisited. It is clear that the clients value the program's work products. Scientists that are conducting work toward LTG 1 are frequently relied on during emergencies. NCEA is consulted regularly for expertise in risk assessment as it relates to each crisis, and the program is doing an admirable job of supporting rapid decision-making. Customers value the LTG 1 products but request more assessments. The Subcommittee members will look for ways to increase efficiency while maintaining quality. Alternatively, more staff can be hired for this effort.

The Subcommittee members classified LTG 2 as "Exceeds Expectations." Dr. Daston stated that the Subcommittee was extremely impressed with the quality of the science products, and appropriate choices are being made in terms of research areas to pursue. Research goals are neither too upstream to be applicable to risk assessment nor too downstream so give insight into the risk assessment process. The work toward LTG 2 translates cutting-edge science into models and methods that can be applied in a consistent way to generate risk assessments. There are clear indications of scientific leadership. The PBPK program is first worldwide in terms of quality, and the BMD methodology is viewed as the gold standard both within and beyond the Agency. The Subcommittee members recommended that the LTG 2 effort evaluate new areas of research and consider hiring senior staff.

The Subcommittee members classified LTG 3 as "Meets Expectations." The effort generates scientifically advanced assessments and meets the needs of the Agency. Dr. Daston stated that the Subcommittee members are optimistic about the changes to the LTG 3 work process and products. They pointed out that efforts to integrate science into the rulemaking for criteria pollutants were exceptional. The LTG 3 efforts have led to proactive approaches to involve the scientific community, interest the stakeholders, and ensure quality. The comprehensive peer-review process occurs at many stages throughout the development of

ISAs. Because the process described under LTG 3 is new to the Agency, the Subcommittee members were not able to assess milestones, but they believe the efforts are properly directed. Dr. Daston recommended that the program increase the transparency of how studies are selected for use in the ISAs. The specific criteria developed for the inclusion or exclusion of various studies in the ISAs should be clear and publicly available. In addition, strategies for identifying gaps in the science that could be addressed before publication of the next ISA should be documented.

Dr. Daston summarized that the review is completely laudatory; the Subcommittee members' recommendations are suggestions for improvements rather than criticisms.

Dr. Daston asked whether the Subcommittee members had additional comments. He confirmed that they did not. He asked if there were additional questions from the participants by telephone. Mr. Adam Sarvana, Inside EPA, asked when the Subcommittee's report would be available. Dr. Daston responded that there is no specific deadline, but the Executive Committee plans to vet the report in January 2008.

Mr. Sarvana asked how the Subcommittee members addressed the fact that OMB restricted NCEA from conducting acute assessments but included the assessments in its performance review. Ms. Foellmer stated that this meeting was not an appropriate forum for that question.

Dr. Daston thanked the participants for their contributions and adjourned the meeting at 11:28 a.m.

Action Items

- ✍ Subcommittee members should submit their completed homework sheets and travel vouchers to Ms. Foellmer.

- ✍ If the Subcommittee members deem it necessary, NCEA staff members will make available a detailed plan of the selection criteria for scientific studies that are used in the ISAs.

- ✍ If the Subcommittee members deem it necessary, Ms. Callahan will provide the Subcommittee members with a list of Region 2 proposed projects for which there has been insufficient funding.

- ✍ Dr. Preuss will estimate the amount of time that NCEA staff members are involved in emergency response. This estimate will be provided to the Subcommittee members.

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APPENDIX A: Meeting Agenda

HHRA SUBCOMMITTEE
FACE-TO-FACE MEETING

Residence Inn Bethesda Downtown
Bethesda, Maryland
November 14–16, 2007

AGENDA

Wednesday, November 14, 2007

8:00 - 8:30 a.m.	Registration	
8:30 - 8:45 a.m.	Welcoming Remarks/ Subcommittee Introduction	Dr. George Daston, Subcommittee Chair
8:45 - 9:00 a.m.	DFO Remarks/Meeting Logistics	Ms. Joanna Foellmer, Subcommittee DFO, ORD
9:00 - 9:15 a.m.	Human Health Risk Assessment: Accomplishing EPA's Mission	Dr. Peter Preuss, ORD Director, NCEA
9:15 - 9:45 a.m.	Overview of LTG 3: - Integrated Science Assessments - Air Quality Criteria Documents	Dr. Ila Cote, ORD, NCEA
9:45 - 11:15 a.m.	Poster Session: LTG 3	
11:15 - 12:00 p.m.	Poster Session Discussion/ Questions on LTG 3	HHRA Subcommittee
12:00 - 1:00 p.m.	Lunch	
1:00 - 1:30 p.m.	Overview of LTG 1: IRIS and Other Priority Health Assessments	Dr. Abdel Kadry, ORD, NCEA
1:30 - 2:45 p.m.	Poster Session: LTG 1	
2:45 - 3:15 p.m.	Poster Session Discussion/ Questions on LTG 1	HHRA Subcommittee

3:15 - 3:30 p.m.	Break	
3:30 - 4:30 p.m.	Program Office Perspectives	Ms. Betsy Southerland, OSWER, OSRTI Ms. Lydia Wegman, OAR, OAQPS
4:30 - 5:00 p.m.	Wrap-Up	Dr. George Daston, Subcommittee Chair
5:00 p.m.	Adjourn	

Thursday, November 15, 2007

10:00 - 10:15 a.m.	Review of Agenda and Day 1	Dr. George Daston, Subcommittee Chair
10:15 - 10:45 a.m.	Overview of LTG 2: Methods, Models and Guidance	Mr. David Bussard, ORD, NCEA
10:45 - 12:15 p.m.	Poster Session: LTG 2	
12:15 - 12:30 p.m.	Public Comment	
12:30 - 1:30 p.m.	Lunch	
1:30 - 2:00 p.m.	Poster Session Discussion/ Questions on LTG 2	HHRA Subcommittee
2:00 - 2:40 p.m.	Regional Prospective	Mr. Kerrigan Clough, DRA, Region 8 Ms. Kathy Callahan, DRA, Region 2
2:40 - 3:00 p.m.	Partnerships/Collaborations	Dr. Tom Burke, Bloomberg School of Public Health, JHU
3:00 - 3:30 p.m.	IRIS User Analysis: Background and Preliminary Results	Mr. Jim Solyst, Environ, Arlington, VA

HHRA Subcommittee Face-To-Face Meeting Agenda
November 14-16, 2007

3:30 - 5:00 p.m.	Subcommittee Working Time	HHRA Subcommittee
5:00 p.m.		Adjourn

Friday, November 16, 2007

8:30 - 11:30 a.m.	Subcommittee Working Time	HHRA Subcommittee
11:30 - 12:00 p.m.	Preliminary Report Out	Dr. George Daston, Subcommittee Chair
12:00 p.m.	Adjourn	